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From: Davis, Minh-Tam
Sent: Wednesday, December 04, 2002 1:50 PM
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Subject: Reprint request for 09/819266

1) Martin, DA, 1998, J Biol Chem, 273(8): 4345-4349
2) Polyakov, V R, 1999, Proceedings Amer Assoc Cancer Res Annual Meeting, 40p729
3) Racke MM, 1999, Society Neurosci Abstracts, 25(1-2): 1585.
Thank you.

MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

636.11

RELEASE OF CASPASE-9 FROM MITOCHONDRIA DURING NEURONAL APOPTOSIS AND CEREBRAL ISCHEMIA. Stanislaw Krajewski*, Maryla Krajewska*, Lisa M. Ellerby*, Kathleen Welsh, Zhihua Xie, Quinn L. Deveraux, Guy S. Salvesen, David E. Bredesen, Barbara Ranscht*, Robert E. Rosenthal#, Carl W. Cotman and John C. Reed. The Burnham Institute, Program on Apoptosis & Cell Death Research Program on Aging Research, 10901 North Torrey Pines Road, La Jolla, CA 92037; *George Washington University School of Medicine, Department of Emergency Medicine, Washington, DC 10021; #The University of Maryland School of Medicine, Department of Anesthesiology Baltimore, MD 21201. @ These two authors contributed equally to the work presented herein.

Caspase-9 is critical for cytochrome c-dependent apoptosis and normal brain development. We determined that this apical protease in the cytochrome c pathway for apoptosis resides inside mitochondria in several types of cells including cardiomyocytes and many neurons. Caspase-9 is released from isolated mitochondria upon treatment with Ca^{2+} or Bax, stimuli implicated in ischemic neuronal cell death that are known to induce cytochrome c release from mitochondria. In neuronal cell culture models, apoptosis-inducing agents trigger translocation of caspase-9 from mitochondria to the nucleus, which is inhibitable by Bcl-2. Similarly, in an animal model of transient global cerebral ischemia, caspase-9 release from mitochondria and apparent accumulation in nuclei was observed in hippocampal and other vulnerable neurons exhibiting early post-ischemic changes preceding apoptosis. Loss of mitochondrial barrier function during neuronal damage from ischemia or other insults therefore may play an important role in making certain caspases and caspase activators (cytochrome c) available to participate in apoptosis.

NIH support (NS 36821, AG 12282, NS 33376, AG 15402, NS 34152).

636.12

CASPASE-3 IS ACTIVATED IN THE HIPPOCAMPUS FOLLOWING SEVERE INSULIN-INDUCED HYPOGLYCEMIA IN THE RAT BRAIN. M. Ferrand-Drake,[1*] J.O. Karlsson,[2] T. Wieloch,[1] K. Blomgren[2]. [1]Laboratory for Experimental Brain Research, Wallenberg Neuroscience Center, University Hospital Lund, 221 85 Lund, Sweden; [2]Department of Physiology, University of Gothenburg, P.O. Box 432, SE 405 30 Gothenburg, Sweden.

Cells in the crest of the hippocampal dentate gyrus are highly vulnerable to a hypoglycemic insult. Mitochondrial permeability transition and subsequent DNA fragmentation has been implicated in the cell death observed in this region. These events are in part mediated by members of the caspase-family which seems to play a central role in mammalian programmed cell death. Caspase-3 is the most studied member and has been strongly implicated even in situations where the traditional morphological criteria for apoptosis are less evident, e.g. following cerebral ischemia. Therefore, we have investigated whether caspase-3 is activated following a hypoglycemic insult to the brain. We used an antibody which recognizes the p17 large fragment of the active complex of caspase-3. In the recovery period, we detect intense immunohistochemical labeling of dentate granule cells which degenerate following 30 minutes of hypoglycemic coma. Furthermore, an assay for measuring the amount of caspase-3 activation was applied. Using protein-extracts from the vulnerable region of the hippocampus a significant rise in activity is seen in the recovery period. We conclude that caspase-3 is activated in the course of hypoglycemic cell death. However, it remains to be established if caspase-activation is a decisive event in hypoglycemic cell death. This work was supported by the Swedish Medical Research Council, the Juvenile Diabetes Foundation International, and the Bergendahl Foundation.

636.13

CASPASE-3 – CALPAIN INTERACTION IN NEONATAL RAT HYPOXIA-ISCHEMIA. K. Blomgren[1,2]*, X. Wang[1], C. Hagelberg[1], J.-O. Karlsson[3], B. Bahr[4], and H. Hagberg[1,5]. [1]Perinatal Center, Inst. of Physiology and Pharmacology, Göteborg Univ., Göteborg, Sweden; [2]Dept. Of Pediatrics, Sahlgrenska Univ. Hospital/Östra, Göteborg, Sweden; [3]Inst. of Anatomy and Cell Biology, Göteborg Univ., Göteborg, Sweden; [4]Dept. of Pharmaceutical Sciences, University of Connecticut, Storrs, CT; [5]Dept. of Obstetrics and Gynecology, Sahlgrenska Univ. Hospital, Göteborg, Sweden.

Hypoxia-ischemia (HI) was induced in 7-day-old rats by left carotid artery occlusion plus 7.7% O_2 for 1 h. Injury develops in the ipsilateral hemisphere whereas the contralateral (hypoxic) hemisphere remains unaffected. Activation (cleavage) of caspase-3 was detectable after 1 h reaching a maximum 24 h post-HI, but only in the ipsilateral hemisphere. The DEVD-cleaving activity followed the same time-course. Pharmacological calpain inhibition (CX295, Cortex Pharmaceuticals, s.c., 40 µmol/kg, every 3 h for 24 h post-HI) inhibited the degradation of fodrin and calpastatin (Blomgren et al., 1999, J. Biol. Chem., 274: 14046-14052). Also, the ratio (ipsilateral/contralateral) of intact caspase-3 changed from 70.3% (vehicle) to 93.8% (CX295) (p=0.005), and the 30 kDa fragment ratio (30/(30+32)) changed from 17.0% (vehicle) to 8.2% (CX295) (p=0.045). However, the degradation of PARP and the DEVD-cleaving activity were not significantly affected, indicating that the presumed calpain-induced cleavage of caspase-3 did not change the activity of this protease. Supported by the Swedish Medical Research Council (12213, 9455).

636.14

CLONING, EXPRESSION, CHARACTERIZATION OF A TETRACYCLINE-DEPENDENT STABLE CELL LINE OVER-EXPRESSING CHIMERIC CASPASE 3 MM Racke[1*], S Na[2], S Kovacevic[2], CS Chang[1], MK Mosior[1], NW Rochm[1]
[1]Dept. Cardiovascular Research, [2]Dept. Research Technologies and Protein, Eli Lilly and Company, Indianapolis, IN 46285

Caspases are known to play an important role in the apoptotic cascade. They are synthesized as inactive proenzymes that are processed by self-proteolysis and/or cleavage by other proteases. Pro-caspase 3 is a 32 kd protein consisting of a small prodomain and 17 kd large subunit and 12 kd small subunit. Cleavage between the prodomain and active subunit, as well as between large and small subunits, generates active heterodimers of large and small subunits and finally forms a tetramer which is then active. Procaspase-3 is a poor inducer of cell death when transfected in mammalian cells, presumably because of its inability to autoactivate. It has been suggested that longer prodomains may be able to mediate dimerization of procaspase molecules, thereby promoting autoprocessing. In an effort to generate highly efficient autoactivating caspase 3, we engineered a chimeric caspase 3 by fusing the caspase 1 prodomain to the caspase 3 catalytic domain. The vector we employed contained neomycin resistance for clonal selection as well as being tetracycline (tet) repressible. By maintaining cells in 1 ug/ml doxycycline during the selection and growth, we kept expression of the potentially lethal chimeric caspase 3 gene tightly regulated. When doxycycline is removed, we observe a time dependent increase in active caspase 3 by immunostaining, *in vitro* caspase 3 enzymatic activity and PARP cleavage. Thus, we were able to generate a stable human neuroblastoma cell line to investigate the role of overexpression of this single caspase. This work indicates that autoactivation of caspase 3 is sufficient to initiate an apoptotic cascade in SK-N-MC cells. It also demonstrates the potential of using a tet-dependent system to study any cell death gene.

Eli Lilly and Company

636.15

EXPRESSION OF THE TR3 DEATH RECEPTOR IN ACUTE AND CHRONIC NEURODEGENERATIVE DISEASE. P. R. Maycox*, B. Crook, J. Meakin, J. Roberts, D. C. Harrison, S. J. Newman* Neuroscience and Analytical Science* Divisions, SB Pharmaceuticals, Third Ave., Harlow, Essex, UK

There is increasing evidence to suggest that the death receptors play a significant role in the removal of neurons both during development and in disease processes. They form a subgroup of the TNFR-superfamily and are characterised by the presence of a cytosolic region known as the death domain, which transduces an apoptotic signal. TR3 is a recently characterised death receptor that is expressed in peripheral tissues and in the fetal and adult brain. Biochemical analysis has shown that TR3 signalling is similar to TNFR1 with initial recruitment of TRADD followed by FADD and caspase 8. The function of TR3, however, is unknown at present and its distribution and expression in the brain has not been studied. In order to characterise the role of death receptors in neurodegeneration, we have analysed the expression patterns of TR3 in the normal and ischemic rat brain. We have analysed modulation of TR3 expression in the pMCAO model of focal ischemia and contrasted changes in TR3 with those observed for three other death receptors that are associated with brain pathology or neuronal elimination , TNFR1, Fas and p75. Our data indicate that the death receptors can be subdivided into groups based on their temporal and regional modulation in the stroke model, suggesting that they play specific and possibly distinct roles in stroke induced cell death. We have further analysed the expression pattern of TR3 in samples from Alzheimer's Disease (AD) patients. There appears to be a specific increase in TR3 in certain neuronal populations in AD cortex and hippocampus.

636.16

CASPASE-2 ACTIVITY MEDIATES NEURONAL CELL DEATH AFTER TRANSIENT GLOBAL CEREBRAL ISCHEMIA. KL. Jin[1*], T. Nagayama[2], DA Greenberg[1], RP Simon[2], and SH. Graham[2]. [1]Buck Center for Research in Aging, Novato, CA94945; [2]Dept. of Neurology, Univ. of Pittsburgh School of Medicine, Pittsburgh, PA15261

Transient global cerebral ischemia induces delayed cell death in the hippocampal CA1 sector. This process of cell death may involve a number of cell death-regulating genes, which include Bcl-2 family genes and caspase family genes.

To investigate whether caspase-2 executes neuronal cell death after transient global ischemia, we identified caspase-2 and caspase-2s cDNAs from a rat ischemic brain cDNA library. Both were highly homologous with the sequences of human and mouse caspase-2 and caspase-2s genes. By RT-PCR, rat caspase-2 and caspase-2s mRNA were upregulated at 8, 24 and 72 hr of reperfusion after global ischemia. The ratio of the two PCR fragments did not change significantly throughout the time course of reperfusion. By analysis of Western blot using a monoclonal antibody against caspase-2, the caspase-2 pro-form was detected in the ischemic as well as non-ischemic hippocampus, and a doublet (28-30 kDa) that may execute cell death, was also detected as early as at 8 hr, and increased with increasing duration of reperfusion. Moreover, administration of the caspase-2 inhibitor (VDVAD-FMK) into the ventricle at 2 hr before ischemia decreased significantly neuronal cell death and reduced DNA damage-positive cells in the CA1 sector at 72 hr after transient global ischemia, suggesting that caspase-2 activation is an important step in programmed neuronal cell death signaling. Therefore, caspase-2 activation may be an additional caspase-related important step in programmed cell death after global ischemia, and may provide a new target for treatment.

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Search Results -

Terms	Documents
caspase near5 (chimer$ or fusion or conjugat$)	37

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Search: L2

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DATE: Wednesday, December 04, 2002 Printable Copy Create Case

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DB=PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR			
L2	caspase near5 (chimer$ or fusion or conjugat$)	37	L2
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L1	caspase near5 (chimer$ or fusion or conjugat$)	19	L1

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☐ 1. Document ID: US 20020176853 A1

L2: Entry 1 of 37 File: PGPB Nov 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020176853
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020176853 A1

TITLE: Card domain containing polypeptides, encoding nucleic acids, and methods of use

PUBLICATION-DATE: November 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Reed, John C.	Rancho Santa Fe	CA	US	
Pio, Frederick F.	Vancouver	CA	CA	
Godzik, Adam	San Diego	CA	US	
Stehlik, Christian	San Diego	CA	US	
Damiano, Jason S.	La Jolla	CA	US	
Lee, Sug Hyung	San Diego	CA	US	
Oliveira, Vasco A.	San Diego		US	
Hayashi, Hideki	Nagasaki City		JP	
Pawlowski, Krzysztof	Malmo		SE	

US-CL-CURRENT: 424/94.63; 435/226, 435/320.1, 435/325, 435/69.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020172958 A1

L2: Entry 2 of 37 File: PGPB Nov 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020172958
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020172958 A1

TITLE: Methods of diagnosing, preventing and treating neurological disorders and neuronal injuries

PUBLICATION-DATE: November 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gonzalez-Zulueta, Mirella	Pacifica	CA	US	
Shamloo, Mehrdad	San Mateo	CA	US	
McFarland, K.C.	Davis	CA	US	
Chin, Daniel	Foster City	CA	US	
Wieloch, Tadeusz	Lund	CA	SE	
Melcher, Thorsten	San Francisco		US	

US-CL-CURRENT: 435/6; 435/7.92

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 20020160975 A1

L2: Entry 3 of 37 File: PGPB Oct 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020160975
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020160975 A1

TITLE: Conserved XIAP-interaction motif in caspase-9 and Smac/DIABLO for mediating apoptosis

PUBLICATION-DATE: October 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Alnemri, Emad S.	Ambler	PA	US	

US-CL-CURRENT: 514/44; 435/184, 435/320.1, 435/325, 435/69.2, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20020159996 A1

L2: Entry 4 of 37 File: PGPB Oct 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020159996
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020159996 A1

TITLE: Use of CD23 antagonists for the treatment of neoplastic disorders

PUBLICATION-DATE: October 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hariharan, Kandasamy	San Diego	CA	US	
Hanna, Nabil	Rancho Santa Fe	CA	US	
Braslawsky, Gary	San Diego	CA	US	
Pathan, Nuzhat	San Diego	CA	US	

US-CL-CURRENT: 424/142.1; 424/144.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 5. Document ID: US 20020156292 A1

L2: Entry 5 of 37 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020156292
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020156292 A1

TITLE: Pyrrole substituted 2-indolinone protein kinase inhibitors

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Tang, Peng Cho	Moraga	CA	US	
Miller, Todd A.	Bend	OR	US	
Li, Xiaoyuan	Los Altos	CA	US	
Sun, Li	Foster City	CA	US	
Wei, Chung Chen	Foster City	CA	US	
Shirazian, Shahrzad	Corte Madera	CA	US	
Liang, Congxin	Sunnyvale	CA	US	
Vojkovsky, Tomas	San Francisco	CA	US	
Nematalla, Asaad S.	Concord	CA	US	
Hawley, Michael	Kalamazoo	MI	US	

US-CL-CURRENT: 548/487

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 6. Document ID: US 20020155579 A1

L2: Entry 6 of 37 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020155579
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020155579 A1

TITLE: Membrane derived caspase-3, compositions comprising the same and methods of use therefor

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Krebs, Joseph F.	San Diego	CA	US	
Srinivasan, Anupama	Carlsbad	CA	US	
Fritz, Lawrence C.	Rancho Santa Fe	CA	US	
Wu, Joe C.	San Diego	CA	US	

US-CL-CURRENT: 435/226; 435/252.3, 435/254.2, 435/320.1, 435/325, 435/348, 435/69.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 20020155505 A1

L2: Entry 7 of 37 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020155505
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020155505 A1

TITLE: Methods for ligand discovery

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wells, Jim	Burlingame	CA	US	
Erlanson, Dan	San Francisco	CA	US	
Braisted, Andrew C.	San Francisco	CA	US	

US-CL-CURRENT: 435/7.1; 530/324, 564/161, 564/192, 564/30, 564/84

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 20020150947 A1

L2: Entry 8 of 37 File: PGPB Oct 17, 2002

PGPUB-DOCUMENT-NUMBER: 20020150947
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020150947 A1

TITLE: Extended tethering approach for rapid identification of ligands

PUBLICATION-DATE: October 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Erlanson, Daniel A.	San Francisco	CA	US	
Braisted, Andrew C.	San Francisco	CA	US	
McDowell, Robert	San Francisco	CA	US	
Prescott, John	San Francisco	CA	US	

US-CL-CURRENT: 435/7.1; 435/6, 436/518

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 9. Document ID: US 20020146804 A1

L2: Entry 9 of 37 File: PGPB Oct 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020146804
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020146804 A1

TITLE: Caspase-14, an apoptotic protease, nucleic acids encoding and methods of use

PUBLICATION-DATE: October 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Alnemri, Emad S.	Ambler	PA	US	
Fernandez-Alnemri, Teresa	Ambler	PA	US	

US-CL-CURRENT: 435/226; 435/320.1, 435/325, 435/69.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 10. Document ID: US 20020132786 A1

L2: Entry 10 of 37 File: PGPB Sep 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020132786
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020132786 A1

TITLE: IAP binding peptide or polypeptide and methods of using the same

PUBLICATION-DATE: September 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Alnemri, Emad S.			US	

US-CL-CURRENT: 514/44; 435/183, 435/320.1, 435/325, 435/69.1, 514/12, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 11. Document ID: US 20020132327 A1

L2: Entry 11 of 37 File: PGPB Sep 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020132327
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020132327 A1

TITLE: METHOD FOR IDENTIFYING PROTEASES, PROTEASE TARGET SITES AND REGULATORS OF PROTEASE ACTIVITY IN CELLS

PUBLICATION-DATE: September 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
HAY, BRUCE A.	PASADENA	CA	US	
HAWKINS, CHRISTINE V.	PARK ORCHARDS		AU	

US-CL-CURRENT: 435/195; 435/183, 435/243, 435/325, 435/4, 435/410, 435/7.1, 530/350, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 12. Document ID: US 20020128219 A1

L2: Entry 12 of 37 File: PGPB Sep 12, 2002

PGPUB-DOCUMENT-NUMBER: 20020128219
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020128219 A1

TITLE: Novel molecules of the card related protein family and uses thereof

PUBLICATION-DATE: September 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bertin, John	Watertown	MA	US	
Alnemri, Emad S.	Ambler	PA	US	

US-CL-CURRENT: 514/44; 435/23, 435/7.9, 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 13. Document ID: US 20020123085 A1

L2: Entry 13 of 37 File: PGPB Sep 5, 2002

PGPUB-DOCUMENT-NUMBER: 20020123085
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020123085 A1

TITLE: Ligand based solution assay for low concentration analytes

PUBLICATION-DATE: September 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Saunders, Alex M.	San Carlos	CA	US	

US-CL-CURRENT: 435/7.92

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 14. Document ID: US 20020110933 A1

L2: Entry 14 of 37 File: PGPB Aug 15, 2002

PGPUB-DOCUMENT-NUMBER: 20020110933
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020110933 A1

TITLE: Arrays of proteins and methods of use thereof

PUBLICATION-DATE: August 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wagner, Peter	Belmont	CA	US	
Ault-Riche, Dana	Palo Alto	CA	US	
Nock, Steffen	Redwood City	CA	US	
Itin, Christian	Menlo Park	CA	US	

US-CL-CURRENT: 436/518; 435/287.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 15. Document ID: US 20020106702 A1

L2: Entry 15 of 37 File: PGPB Aug 8, 2002

PGPUB-DOCUMENT-NUMBER: 20020106702
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020106702 A1

TITLE: Protein arrays for high-throughput screening

PUBLICATION-DATE: August 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wagner, Peter	Cupertino	CA	US	
Ault-Riche, Dana	Palo Alto	CA	US	
Nock, Steffen	Palo Alto	CA	US	
Itin, Christian	Menlo Park	CA	US	

US-CL-CURRENT: 435/7.9; 435/287.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 16. Document ID: US 20020106631 A1

L2: Entry 16 of 37 File: PGPB Aug 8, 2002

PGPUB-DOCUMENT-NUMBER: 20020106631
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020106631 A1

TITLE: Recombinant, active caspases and uses thereof

PUBLICATION-DATE: August 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Alnemri, Emad S.	Ambler	PA	US	

US-CL-CURRENT: 435/4; 435/23, 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 17. Document ID: US 20020102726 A1

L2: Entry 17 of 37 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020102726
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020102726 A1

TITLE: Immortalized human keratinocyte cell line

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Allen-Hoffmann, B. Lynn	Madison	WI	US	

US-CL-CURRENT: 435/325; 435/235.1, 435/347, 435/371, 435/373, 435/402, 435/408, 435/5, 435/6, 435/7.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 18. Document ID: US 20020081705 A1

L2: Entry 18 of 37 File: PGPB Jun 27, 2002

PGPUB-DOCUMENT-NUMBER: 20020081705
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020081705 A1

TITLE: Human caspase-14 compositions

PUBLICATION-DATE: June 27, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mankovich, John A.	Andover	MA	US	

US-CL-CURRENT: 435/226; 435/23, 435/325, 435/69.1, 435/7.92, 530/388.26, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 19. Document ID: US 20020073441 A1

L2: Entry 19 of 37 File: PGPB Jun 13, 2002

PGPUB-DOCUMENT-NUMBER: 20020073441
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020073441 A1

TITLE: Compositions and methods for detecting proteolytic activity

PUBLICATION-DATE: June 13, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ross, Brian D.	Ann Arbor	MI	US	
Rehemtulla, Alnawaz	Plymouth	MI	US	

US-CL-CURRENT: 800/18; 435/189, 435/354, 435/4, 530/350, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 20. Document ID: US 20020049251 A1

L2: Entry 20 of 37 File: PGPB Apr 25, 2002

PGPUB-DOCUMENT-NUMBER: 20020049251
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020049251 A1

TITLE: Methods for treating cell death diseases and inflammation

PUBLICATION-DATE: April 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Yang, Zhen	Brookline	MA	US	
Kobori, Masuko	Ibaraki	MA	JP	
Yuan, Junying	Newton		US	

US-CL-CURRENT: 514/453; 424/725, 549/276

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 21. Document ID: US 20020037280 A1

L2: Entry 21 of 37 File: PGPB Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037280
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020037280 A1

TITLE: Recombinant, modified adenoviral vectors for tumor specific gene expression and uses thereof

PUBLICATION-DATE: March 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lieber, Andre	Seattle	WA	US	
Steinwaerder, Dirk S.	Hamburg	WA	DE	
Carlson, Cheryl A.	Seattle	WA	US	
Mi, Jie	Seattle		US	

US-CL-CURRENT: 424/93.21; 435/235.1, 435/320.1, 435/456

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 22. Document ID: US 20020034812 A1

L2: Entry 22 of 37 File: PGPB Mar 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020034812
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020034812 A1

TITLE: Caspase homologue

PUBLICATION-DATE: March 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Craen, Marc van de	Gent		BE	
Declercq, Wim	Marke		BE	
Vandenabeele, Peter	Sint-Amandsberg		BE	
Fiers, Walter	Destelbergen		BE	

US-CL-CURRENT: 435/226; 435/320.1, 435/325, 435/69.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 23. Document ID: US 20020028178 A1

L2: Entry 23 of 37 File: PGPB Mar 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020028178
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020028178 A1

TITLE: Treatment of B cell malignancies using combination of B cell depleting antibody and immune modulating antibody related applications

PUBLICATION-DATE: March 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	
Hariharan, Kandasamy	San Diego	CA	US	

US-CL-CURRENT: 424/1.49; 424/143.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 24. Document ID: US 20020010203 A1

L2: Entry 24 of 37 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020010203
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020010203 A1

TITLE: Methods of modulating c-kit tyrosine protein kinase function with indolinone compounds

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lipson, Ken	San Mateo	CA	US	
McMahon, Gerald	Kenwood	CA	US	

US-CL-CURRENT: 514/418

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 25. Document ID: US 20020009757 A1

L2: Entry 25 of 37 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020009757
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020009757 A1

TITLE: Screening assays for agents that alter inhibitor of apoptosis (IAP) protein

regulation of caspase activity

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Reed, John C.	Rancho Santa Fe	CA	US	
Deveraux, Quinn	San Diego	CA	US	
Salvesen, Guy S.	Encinitas	CA	US	
Takahashi, Ryosuke	San Diego	CA	US	
Roy, Natalie	La Jolla	CA	US	

US-CL-CURRENT: 435/7.23; 435/23

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 26. Document ID: US 20020006404 A1

L2: Entry 26 of 37 File: PGPB Jan 17, 2002

PGPUB-DOCUMENT-NUMBER: 20020006404
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020006404 A1

TITLE: Treatment of cell malignancies using combination of B cell depleting antibody and immune modulating antibody related applications

PUBLICATION-DATE: January 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	
Hariharan, Kandasamy	San Diego	CA	US	

US-CL-CURRENT: 424/142.1; 424/155.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 27. Document ID: US 20010041681 A1

L2: Entry 27 of 37 File: PGPB Nov 15, 2001

PGPUB-DOCUMENT-NUMBER: 20010041681
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010041681 A1

TITLE: Therapeutically useful synthetic oligonucleotides

PUBLICATION-DATE: November 15, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Phillips, Nigel C.	Point-Claire		CA	
Filion, Mario C.	Laval		CA	

US-CL-CURRENT: 514/44; 514/171

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 28. Document ID: US 20010018195 A1

L2: Entry 28 of 37 File: PGPB Aug 30, 2001

PGPUB-DOCUMENT-NUMBER: 20010018195
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010018195 A1

TITLE: Screening assays for agents that alter inhibitor of apoptosis (IAP) protein regulation of caspase activity

PUBLICATION-DATE: August 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Reed, John C.	Rancho Santa Fe	CA	US	
Deveraux, Quinn	San Diego	CA	US	
Salvesen, Guy S.	Encinitas	CA	US	
Takahashi, Ryosuke	San Diego	CA	US	
Roy, Natalie	La Jolla	CA	US	

US-CL-CURRENT: 435/18; 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 29. Document ID: US 20010018041 A1

L2: Entry 29 of 37 File: PGPB Aug 30, 2001

PGPUB-DOCUMENT-NUMBER: 20010018041
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010018041 A1

TITLE: Treatment of B cell malignancies using anti-CD40L antibodies in combination with anti-CD20 antibodies and/or chemotherapeutics and radiotherapy

PUBLICATION-DATE: August 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	
Hariharan, Kandasamy	San Diego	CA	US	

US-CL-CURRENT: 424/1.49; 424/181.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 30. Document ID: US 20010011078 A1

L2: Entry 30 of 37 File: PGPB Aug 2, 2001

PGPUB-DOCUMENT-NUMBER: 20010011078
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010011078 A1

TITLE: DNA fragmentation factor involved in apoptosis

PUBLICATION-DATE: August 2, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wang, Xiaodong	Dallas	TX	US	
Liu, Xueson	Dallas	TX	US	

US-CL-CURRENT: 514/44; 424/93.2, 424/94.6, 435/196, 435/320.1, 435/6, 530/388.26, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

Generate Collection | Print

Terms	Documents
caspase near5 (chimer$ or fusion or conjugat$)	37

Display Format: - Change Format

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In situ activation of caspases and serine proteases during apoptosis detected by affinity labeling their enzyme active centers with fluorochrome-tagged inhibitors.

Grabarek Jerzy; Darzynkiewicz Zbigniew; et al
Brander Cancer Research Institute at New York Medical College, Valhalla, NY, USA

Experimental hematology (Netherlands) Sep 2002, 30 (9) p982-9, ISSN 0301-472X Journal Code: 0402313
Contract/Grant No.: R01 28 704; PHS; +
Document type: Journal Article; Review; Review of Reported Cases
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

8/10

Activation of caspases is the key event of apoptosis. To detect this event in situ we applied fluorochrome-labeled inhibitors of caspases (FLICA) as affinity labels of active centers of these enzymes. The FLICA are fluorescein- or sulforhodamine-conjugated peptide-fluoromethyl ketones that covalently, with 1:1 stoichiometry, **bind** to enzymatic centers of caspases; the specificity is provided by the peptide sequence of amino acids. Similarly, we applied fluorescent **inhibitors** of serine **proteases** (FLISP) to detect active sites of the latter enzymes. Exposure of live cells to FLICA of FLISP led to uptake of these ligands and their **binding** to **activated caspases** or active sites of serine proteases; the unbound reagents were removed by cell rinse. Only cells undergoing apoptosis were labeled with FLISP or FLICA. Intracellular **binding** sites of FLICA are consistent with known localization of caspases. Covalent **binding** of FLICA or FLISP allowed us to identify the labeled proteins by immunoblotting: the proteins that bound individual FLICAs had molecular weight between 17 and 22 kDa, which corresponds to large subunits of the caspases; two proteins reacting with FLISP were about 57 and 60 kDa, which suggests that they are novel enzymes. Detection of caspases or serine proteases activation can be combined with other markers of apoptosis or cell cycle for multiparametric analysis by flow or laser scanning cytometry. Being caspase inhibitors, FLICA arrest the process of apoptosis and prevent cell disintegration. The stathmo-apoptotic assay was developed, therefore, to obtain cumulative apoptotic index over a long period of time and estimate a rate of cell entry into apoptosis for cell populations.

... FLICA are fluorescein- or sulforhodamine-conjugated peptide-fluoromethyl ketones that covalently, with 1:1 stoichiometry, **bind** to enzymatic centers of caspases; the specificity is provided by the peptide sequence of amino acids. Similarly, we applied fluorescent **inhibitors** of serine **proteases** (FLISP) to detect active sites of the latter enzymes. Exposure of live cells to FLICA of FLISP led to uptake of these ligands and their **binding** to **activated caspases** or active sites of serine proteases; the unbound reagents were removed by cell rinse. Only cells undergoing apoptosis were labeled with FLISP or FLICA. Intracellular **binding** sites of FLICA are consistent with known localization of caspases. Covalent **binding** of FLICA or FLISP allowed us to identify the labeled proteins by immunoblotting: the proteins...

; Affinity Labels--diagnostic use--DU; **Binding** Sites; Biotinylation ; Caspases--chemistry--CH; Cell Cycle; Cells, Cultured--enzymology--EN; Cysteine Proteinase Inhibitors--analysis...

14198274 22314698 PMID: 12427028

A highly conserved arginine is critical for the functional folding of inhibitor of apoptosis (IAP) BIR domains.

Luque Laura E; Grape Katrina P; Junker Matthew; et al

Department of Molecular and Cell Biology, University of Texas at Dallas, P.O. Box 830688, Richardson, Texas 75083-0688, USA.

Biochemistry (United States) Nov 19 2002, 41 (46) p13663-71, ISSN 0006-2960 Journal Code: 0370623

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The inhibitor of apoptosis (IAP) proteins are found in all animals and regulate apoptosis (programmed cell death) by binding and inhibiting caspase proteases. This inhibition is overcome by several apoptosis stimulators, including Drosophila Hid and mammalian Smac/DIABLO, which bind to 65-residue baculovirus IAP repeat (BIR) domains found in one to three copies in all IAPs. Virtually all BIRs contain three Cys and a His that bind zinc, a Gly in a tight turn, and an Arg. The functional and structural role of the Arg was investigated in isolated BIR domains from the baculovirus Orgyia pseudotsugata Op-IAP and the Drosophila DIAP1 proteins. Mutation of the Arg to either Ala or Lys abolished Hid and Smac binding to BIRs, despite the Hid/Smac binding site being **located** on the opposite side of the BIR domain from the Arg. The mutant BIR domains also exhibited weakened zinc binding, increased sensitivity to limited proteolysis, and altered circular dichroism spectra indicative of perturbed domain folding. Examination of known BIR structures indicates that the Arg side chain makes simultaneous bridging hydrogen bonds and a cation-pi interaction for which the Arg guanidino group is uniquely well suited. These interactions are likely critical for stabilizing the tertiary fold of BIR domains in all IAPs, explaining the conservation of this residue.

p1-9, ISSN 0168-8227 Journal Code: 8508335
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process

The pathogenesis of pericyte loss, an initial deficit in the early stage of diabetic retinopathy, remains unclear. Recent studies have suggested that polyol pathway hyperactivity and apoptosis may be involved in pericyte loss. The mechanisms of the glucose-induced apoptosis in retinal pericytes were investigated to evaluate the pathogenesis of diabetic retinopathy. Under the 20 mM glucose condition, intracellular calcium concentrations and caspase-3 activities were significantly increased, and reduced glutathione (GSH) contents were significantly decreased compared with those under the 5.5 mM glucose condition. These abnormalities were all significantly prevented by an aldose reductase inhibitor, SNK-860. Glucose-induced apoptosis was partially but significantly prevented by SNK-860, an inhibitor of calcium-dependent cysteine protease, calpain,

06362837 Genuine Article#: YM353 Number of References: 64
Title: The c-IAP-1 and c-IAP-2 proteins are direct inhibitors of specific caspases (ABSTRACT AVAILABLE)
Author(s): Roy N; Deveraux QL; Takahashi R; Salvesen GS; Reed JC (REPRINT)

Corporate Source: BURNHAM INST,PROGRAM APOPTOSIS & CELL DEATH RES, 10901 N TORREY PINES RD/LA JOLLA//CA/92037 (REPRINT); BURNHAM INST,PROGRAM APOPTOSIS & CELL DEATH RES/LA JOLLA//CA/92037
Journal: EMBO JOURNAL, 1997, V16, N23 (DEC 1), P6914-6925
ISSN: 0261-4189 Publication date: 19971201
Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD, ENGLAND OX2 6DP
Language: English Document Type: ARTICLE
Abstract: The inhibitor of apoptosis (IAP) family of proteins are highly conserved through evolution, However, the mechanisms by which these proteins interfere with apoptotic cell death have been enigmatic, Recently, we showed that one of the human IAP family proteins, XIAP, can **bind** to and potently inhibit specific cell death proteases (caspases) that function in the distal portions of the proteolytic cascades involved in apoptosis, In this study, we investigated three of the other known members of the human IAP family, c-IAP-1, c-IAP-2 and NAIP, Similarly to XIAP, in vitro **binding** experiments indicated that c-IAP-1 and c-IAP-2 bound specifically to the terminal effector cell death proteases, caspases-3 and -7, but not to the proximal protease caspase-8, caspases-1 or -6, In contrast, NAIP failed to **bind** tightly to any of these proteases, Recombinant c-IAP-1 and c-IAP-2 also inhibited the activity of caspases-3 and -7 in vitro, with estimated K(i)s of less than or equal to 0.1 mu M, whereas NAIP did not, The BIR domain-containing region of c-IAP-1 and c-IAP-2 was sufficient for inhibition of these caspases, though proteins that retained the RING domain were somewhat more potent, Utilizing a cell-free system in which **caspases** were **activated** in cytosolic extracts by addition of cytochrome c, c-IAP-1 and c-IAP-2 inhibited both the generation of caspase activities and proteolytic processing of pro-caspase-3, Similar results were obtained in intact cells when c-IAP-1 and c-IAP-2 were overexpressed by gene transfection, and apoptosis was induced by the anticancer drug, etoposide, Cleavage of c-IAP-1 or c-IAP-2 was not observed when interacting with the caspases, implying a different mechanism from the baculovirus p35 protein, the broad spectrum suicide inactivator of caspases, Taken together, these findings suggest that c-IAP-1 and c-IAP-2 function similarly to XIAP by inhibiting the distal cell death proteases, caspases-3 and -7, whereas NAIP presumably inhibits apoptosis via other targets.
...Abstract: been enigmatic, Recently, we showed that one of the human IAP family proteins, XIAP, can **bind** to and potently inhibit specific cell death proteases (caspases) that function in the distal portions...

...IAP family, c-IAP-1, c-IAP-2 and NAIP, Similarly to XIAP, in vitro **binding** experiments indicated that c-IAP-1 and c-IAP-2 bound specifically to the terminal...

...to the proximal protease caspase-8, caspases-1 or -6, In contrast, NAIP failed to **bind** tightly to any of these proteases, Recombinant c-IAP-1 and c-IAP-2 also...

...retained the RING domain were somewhat more potent, Utilizing a

09742623 Genuine Article#: 442RC Number of References: 51
Title: Abrin triggers cell death by inactivating a thiol-specific antioxidant protein (ABSTRACT AVAILABLE)
Author(s): Shih SF; Wu YH; Hung CH; Yang HY; Lin JY (REPRINT)
Corporate Source: Natl Taiwan Univ,Coll Med, Inst Biochem & Mol Biol,Taipei 10081//Taiwan/ (REPRINT); Natl Taiwan Univ,Coll Med, Inst Biochem & Mol Biol,Taipei 10081//Taiwan/
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 2001, V276, N24 (JUN 15), P 21870-21877
ISSN: 0021-9258 Publication date: 20010615
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA
Language: English Document Type: ARTICLE
Abstract: Abrin A-chain (ABRA) inhibits protein synthesis by its N-glycosidase activity as well as induces **apoptosis**, but the molecular mechanism of ABRA-induced cell death has been obscure. Using an ABRA mutant that lacks N-glycosidase activity as bait in a yeast two-hybrid system, a 30-kDa antioxidant protein-1 (AOP-1) was found to be an ABRA(E164Q)-interacting protein. The interaction was further confirmed in vitro by a glutathione S-transferase pull-down assay. The colocalization of endogenous AOP-1 and exogenous ABR proteins in the cell was demonstrated by confocal immunofluorescence, We also demonstrated that ABRA attenuates AOP-1 antioxidant activity in a dose-dependent manner and the intracellular level of reactive oxygen species (ROS) increases in ABR-treated cells. Moreover, ROS scavengers N-acetylcysteine and 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl delayed programmed cell death. This indicates that ROS are important mediators of ABR-induced **apoptosis**, When ectopically expressed, AOP-1 blocked the release of cytochrome c and prevented **apoptosis** in ABR-treated cells. These findings suggest that the binding of ABRA to AOP-1 promotes **apoptosis** by inhibiting the mitochondrial antioxidant protein AOP-1, resulting in the increase of intracellular ROS and the release of cytochrome c from the mitochondria to the cytosol, which activates **caspase**-9 and **caspase**-3.

Dialog Acc No: 1861628 IFI Acc No: 8811560
Document Type: C
MONOCLONAL ANTI-HUMAN BREAST **CANCER** ANTIBODIES; INCUBATION OF CELL WITH MURINE ANTIBODY, DIAGNOSIS; SELECTIVE BINDING, RICIN CONJUGATES
Inventors: BJORN MICHAEL J (US); FRANKEL ARTHUR E (US); RING DAVID B (US)
Assignee: CETUS CORP
Assignee Code: 15428 Document Type: REASSIGNED
Publication (No,Date), Applic (No,Date):
US 4753894 19880628 US 85690750 19850111
Publication Kind: A
Calculated Expiration: 20050628
(Cited in 040 later patents)
Cont.-in-part Pub(No),Applic(No,Date): ABANDONED US 84577976 19840208
Priority Applic(No,Date): US 85690750 19850111; US 84577976 19840208

Abstract: Murine monoclonal antibodies are prepared and characterized which bind selectively to human breast **cancer** cells, are IgGs or IgMs, and when conjugated to ricin A chain, exhibit a TCID 50% against at least one of MCF-7, CAMA-1, SKBR-3, or BT-20 cells of less than about 10 nM. Methods for diagnosing, monitoring, and treating human breast **cancer** with the antibodies or immunotoxins made therefrom are described.

12/04

4/3,K,AB/18 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06509402 Genuine Article#: YY117 Number of References: 32
Title: Membrane oligomerization and cleavage activates the caspase-8 (FLICE/MACH alpha 1) death signal (ABSTRACT AVAILABLE)
Author(s): Martin DA; Siegel RM; Zheng LX; Lenardo MJ (REPRINT)
Corporate Source: NIAID,IMMUNOL LAB, NIH, RM 11N311, BLDG 10, 10 CTR DR, MSC1892/BETHESDA//MD/20892 (REPRINT); NIAID,IMMUNOL LAB, NIH/BETHESDA//MD/20892
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1998, V273, N8 (FEB 20), P 4345-4349
ISSN: 0021-9258 Publication date: 19980220
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Abstract: Many forms of apoptosis, including that caused by the death receptor CD95/Fas/APO-1, depend on the activation of caspases, which are proteases that cleave specific intracellular proteins to cause orderly cellular disintegration. The requirements for activating these. crucial enzymatic mediators of death are not well understood. Using molecular chimeras with either CD8 or Tac, we find that oligomerization at the cell membrane powerfully induces caspase-8 autoactivation and apoptosis. Death induction was abrogated by the z-VAD-fmk, z-IETD-fmk, or p35 enzyme inhibitors or by a mutation in the active site cysteine but was surprisingly unaffected by death inhibitor Bcl-2, Amino acid substitutions that prevent the proteolytic separation of the caspase from its membrane-associated domain completely blocked apoptosis. Thus, oligomerization at the membrane is sufficient for caspase-8 autoactivation, but apoptosis could involve a death signal conveyed by the proteolytic release of the enzyme into the cytoplasm.

...Abstract: chimeras with either CD8 or Tac, we find that oligomerization

12/04

18/3,K,AB/28 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

11941353 BIOSIS NO.: 199900187462
Membrane permeant peptide **conjugates** for imaging **caspase**-3 activity in vivo.
AUTHOR: Polyakov V R; Dahlheimer J; Piwnica-Worms D
AUTHOR ADDRESS: Washington Univ. Med. Sch., St. Louis, MO 63110**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p729 March, **1999**
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999

Membrane permeant peptide **conjugates** f

12/04

18/3,K,AB/27 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

12456077 BIOSIS NO.: 200000209579
Cloning, expression, characterization of a tetracycline-dependent stable cell line over-expressing **chimeric caspase** 3.
AUTHOR: Racke M M(a); Na S; Kovacevic S; Chang C S(a); Mosior M K(a); Roehm N W(a)
AUTHOR ADDRESS: (a)Dept. Cardiovascular Research, Eli Lilly and Company, Indianapolis, IN, 46285**USA
JOURNAL: Society for Neuroscience Abstracts 25 (1-2):p1585 **1999**
CONFERENCE/MEETING: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
1999

Cloning, expression, characterization

18/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10835293 20391256 PMID: 10356366

GAL4 is a substrate for caspases: implications for two-hybrid screening and other GAL4-based assays.

van Criekinge W; Cornelis S; Van De Craen M; Vandenabeele P; Fiers W; Beyaert R

Department of Molecular Biology, Flanders Interuniversity Institute for Biotechnology and University of Ghent, Belgium.

Molecular cell biology research communications : MCBRC (UNITED STATES) May **1999**, 1 (2) p158-61, ISSN 1522-4724 Journal Code: 100889076

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Yeast two-hybrid technology as well as mammalian reporter assays use fusions between a protein of interest and the GAL4 DNA-binding domain (GAL4DB). We demonstrate that expression of a GAL4DB/**caspase**-1 **chimeric** protein in yeast leads to autoproteolytic cleavage of GAL4DB. Moreover, recombinant GAL4DB is a good in vitro substrate for recombinant caspase-1 and several other caspases. Cleavage sites map at the C-terminus of GAL4DB and result in release of the fused protein. The finding that GAL4DB can be cleaved by caspases has important implications for the use of caspases in two-hybrid analysis and in the interpretation of mammalian assays based on GAL4-dependent reporter gene expression.

```
? ds

Set     Items   Description
S1      33376   CASPASE??
S2    1566112   CONJUGAT? OR FUSED OR FUSION OR LINK?
S3       3180   S1 AND S2
S4    2244530   LIGAND OR ANTIBOD? OR TARGET?
S5       1171   S3 AND S4
S6    1349719   ANTIBOD?
S7        497   S3 AND S6
S8        259   S7 AND PY<=2000
S9         54   S8 AND PY=1999
S10       118   S8 AND PY<=1999
S11        71   RD (unique items)
S12       136   CASPASE?? (5N)(CONJUGAT? OR FUSED OR FUSION)
S13        83   S12 AND PY<=2000
S14        34   S13 AND S4
S15        20   RD (unique items)
? s caspase??(2n)(conjugat? or fused or fusion or chimer?)
          33376  CASPASE??
         230535  CONJUGAT?
          93807  FUSED
         271198  FUSION
          84648  CHIMER?
     S16      84  CASPASE??(2N)(CONJUGAT? OR FUSED OR FUSION OR CHIMER?)
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...completed examining records
     S17      53  RD (unique items)
```

10944870 20504499 PMID: 11050246

Intracellular **antibody**-caspase-mediated cell killing: an approach for application in cancer therapy.

Tse E; Rabbitts T H

Medical Research Council Laboratory of Molecular Biology, Division of Protein and Nucleic Acid Chemistry, Hills Road, Cambridge CB2 2QH, United Kingdom.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 24 **2000**, 97 (22) p12266-71, ISSN 0027-8424 Journal Code: 7505876

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Antibodies have been expressed inside cells in an attempt to ablate the function of oncogene products. To make intracellular **antibodies** more generally applicable and effective in cancer therapy, we have devised a method in which programmed cell death or apoptosis can be triggered by specific **antibody**-antigen interaction. When intracellular **antibodies** are linked to caspase 3, the "executioner" in the apoptosis pathway, and bind to the **target** antigen, the caspase 3 moieties are self-activated and thereby induce cell killing. We have used this strategy in a model system with two pairs of intracellular **antibodies** and antigens. In vivo coexpression of an **antibody-caspase** 3 **fusion** with its antigenic **target** induced apoptosis that was specific for **antibody**, antigen, and active caspase 3. Moreover, the **antibody-caspase** 3 **fusion** protein was not toxic to cells in the absence of antigen. Therefore, intracellular **antibody** -mediated apoptosis should be useful as a specific therapeutic approach for the treatment of cancers, a situation where **target** cell killing is required.

nterleukin 1 receptor antagonist protein; DNA; **Caspase** 1
? ds

```
Set     Items   Description
S1      33376   CASPASE??
S2    1566112   CONJUGAT? OR FUSED OR FUSION OR LINK?
S3       3180   S1 AND S2
S4    2244530   LIGAND OR ANTIBOD? OR TARGET?
S5       1171   S3 AND S4
S6    1349719   ANTIBOD?
S7        497   S3 AND S6
S8        259   S7 AND PY<=2000
S9         54   S8 AND PY=1999
S10       118   S8 AND PY<=1999
S11        71   RD (unique items)
? s caspase?? (5n)(conjugat? or fused or fusion)
          33376  CASPASE??
         230535  CONJUGAT?
          93807  FUSED
         271198  FUSION
     S12     136  CASPASE?? (5N)(CONJUGAT? OR FUSED OR FUSION)
? s s12 and py<=2000
Processing
Processing
            136  S12
       37910018  PY<=2000
     S13      83  S12 AND PY<=2000
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             83  S13
        2244530  S4
     S14      34  S13 AND S4
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>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
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     S15      20  RD (unique items)
? t s15/3,k,ab/1-20

 15/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11029428   21020962   PMID: 11140638
  Structural basis of IAP recognition by Smac/DIABLO.
  Wu G; Chai J; Suber T L; Wu J W; Du C; Wang X; Shi Y
  Department of Molecular Biology, Princeton University, New Jersey 08544,
USA.
  Nature (England)   Dec 21-28 2000,  408   (6815)  p1008-12,  ISSN
0028-0836   Journal Code: 0410462
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Apoptosis is an essential process in the development and homeostasis of
all metazoans. The inhibitor-of-apoptosis (IAP) proteins suppress cell
death by inhibiting the activity of caspases; this inhibition is performed
by the zinc-binding BIR domains of the IAP proteins. The mitochondrial
protein Smac/DIABLO promotes apoptosis by eliminating the inhibitory effect
of IAPs through physical interactions. Amino-terminal sequences in
Smac/DIABLO are required for this function, as mutation of the very first
amino acid leads to loss of interaction with IAPs and concomitant loss of
Smac/DIABLO function. Here we report the high-resolution crystal structure
of Smac/DIABLO complexed with the third BIR domain (BIR3) of XIAP. Our
results show that the N-terminal four residues (Ala-Val-Pro-Ile) in
```

Smac/DIABLO recognize a surface groove on BIR3, with the first residue Ala binding a hydrophobic pocket and making five hydrogen bonds to neighbouring residues on BIR3. These observations provide a structural explanation for the roles of the Smac N terminus as well as the conserved N-terminal sequences in the Drosophila proteins Hid/Grim/Reaper. In

Flow cytometry detection of caspase 3 activation in preapoptotic leukemic cells.

Belloc F; Belaud-Rotureau M A; Lavignolle V; Bascans E; Braz-Pereira E; Durrieu F; Lacombe F

Laboratoire d'Hematologie, Hopital Haut Leveque, Pessac, France. francis.belloc@wanadoo.fr

Cytometry : the journal of the Society for Analytical Cytology (UNITED STATES) Jun 1 **2000**, 40 (2) p151-60, ISSN 0196-4763
Journal Code: 8102328

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Procaspase 3 is a constitutive proenzyme that is activated by cleavage during apoptosis. The resulting enzyme is able to cleave several **target** proteins after the second aspartate of a DEVD sequence common to all the substrates of caspases 3 and 7 (DEVDase). Because active caspase 3 is a common effector in several apoptotic pathways, it may be a good marker to detect (pre-)apoptotic cells by flow cytometry (FCM). Materials and Methods Apoptosis was induced in U937 or bone marrow mononuclear cells by daunorubicin (DNR), idarubicin (IDA), or camptothecin (CAM). Viable and apoptotic cells were sorted by FCM on the basis of either fluorescein isothiocyante (FITC)-annexin V binding or DiOC6(3) accumulation. DEVDase activity was measured in sorted populations by spectrofluorometry. Cleaved caspase 3 was labeled in situ with phycoerythrin (PE)-**conjugated** anti-activated **caspase** 3 **antibodies** and analyzed by FCM. RESULTS: DEVDase activity was detected in sorted viable CAM- and DNR-treated U937 cells, demonstrating that a partial caspase activation occurred earlier than phosphatidyl-serine exposure and mitochondrial membrane potential dissipation. The presence of a low amount of active caspase 3 in the treated viable cells was confirmed in situ with PE-**conjugated** anti-active **caspase** 3 **antibodies**. The same **antibody** was used in combination with FITC-annexin V and CD45-PC5 to study caspase 3 activation in acute leukemia blast cells after in vitro DNR

ialog Acc No: 1917996 IFI Acc No: 8903411
Document Type: C
MONOCLONAL ANTIBODY AGAINST OVARIAN **CANCER** CELLS (OVB-3);
CELL-SPECIFIC; ANTITUMOR AND ANTICARCINOGENIC AGENTS
Inventors: FITZGERALD DAVID J (US); PASTAN IRA (US); WILLINGHAM MARK (US)
Assignee: U S OF AMERICA HEALTH & HUMAN SERVICES
Assignee Code: 06814
Publication (No,Date), Applic (No,Date):
US 4806494 19890221 US 86888960 19860724
Publication Kind: A
Calculated Expiration: 20060724
(Cited in 007 later patents) Document Type: EXPIRED
Priority Applic(No,Date): US 86888960 19860724

Abstract: Monoclonal antibodies are produced which specifically bind to human ovarian **cancer** cells. These antibodies are conjugated to Pseudomonas exotoxin in order to produce an **immunotoxin** suitable for the chemotherapeutic treatment of human ovarian **cancer**.

MONOCLONAL ANTIBODY AGAINST OVARIAN **CANCER** CELLS (OVB-3...

```
STEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Nov W3
*File 155: For updating information please see Help News155. Alert
feature enhanced with customized scheduling. See HELP ALERT.
  File  55:Biosis Previews(R)  1993-2002/Nov W4
        (c) 2002 BIOSIS
*File  55: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File  34:SciSearch(R) Cited Ref Sci  1990-2002/Dec W1
        (c) 2002 Inst for Sci Info
*File  34: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File 434:SciSearch(R) Cited Ref Sci  1974-1989/Dec
        (c) 1998 Inst for Sci Info
  File 340:CLAIMS(R)/US Patent  1950-02/Nov 28
        (c) 2002 IFI/CLAIMS(R)
*File 340: Application & grant publications are in 1 record. See
 HELP NEWS340 & HELP ALERTS340 for search, display & Alert info.

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           84648  CHIMER?
           33376  CASPASE??
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>>>Duplicate detection is not supported for File 340.

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Processing
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3/3,K,AB/45 (Item 6 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

12471441 BIOSIS NO.: 200000224943
A nonviral gene delivery system to target breast cancer and metastases.
AUTHOR: Zou Yiyu(a); Peng H(a); Wen Y(a); Zhou B P(a); Zhang S(a); Hung M C (a)
AUTHOR ADDRESS: (a)UT M D Anderson Cancer Ctr, Houston, TX**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p452 March, 2000
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

A nonviral gene delivery system to target breast cancer and metastases.
2000
...REGISTRY NUMBERS: CASPASE-3
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...caspase-3

9800311 98221134 PMID: 9553057

Generation of constitutively active recombinant caspases-3 and -6 by rearrangement of their subunits.

Srinivasula S M; Ahmad M; MacFarlane M; Luo Z; Huang Z; Fernandes-Alnemri T; Alnemri E S

Center for Apoptosis Research and the Department of Microbiology and Immunology, Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.

Journal of biological chemistry (UNITED STATES) Apr 24 1998, 273 (17) p10107-11, ISSN 0021-9258 Journal Code: 2985121R

Contract/Grant No.: AG13487; AG; NIA

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

12/04

Caspases play a major role in the transduction of the apoptotic signal and execution of apoptosis in mammalian cells. Ectopic overexpression of the short prodomain caspases-3 and -6 precursors in mammalian cells does not induce apoptosis. This is due to their inability to undergo autocatalytic processing/activation and suggests that they depend on the long prodomain caspases for activation. To investigate directly the apoptotic activity of these two caspases in vivo, we engineered constitutively active recombinant caspases -3 and -6 precursors. This was achieved by making contiguous precursor caspases -3 and -6 molecules, which have their small subunits preceding their large subunits. Unlike their wild type counterparts, these recombinant molecules were capable of autocatalytic processing in an in vitro translation reaction, suggesting that they are catalytically active. They were also capable of autoprocessing and inducing apoptosis in vivo independent of the upstream caspases . Furthermore, their autocatalytic and apoptotic activities were inhibited by the pancaspase inhibitor z-VAD-fluoromethylketone, but not by CrmA or Bcl-2, thus directly demonstrating that the targets of inhibition of apoptosis by CrmA and Bcl-2 are upstream of caspases-3 and -6. Since caspases-3 and -6 are the most downstream executioners of apoptosis, the constitutively active versions of these caspases could be used at very low concentrations

3/3,K,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10220447 99201819 PMID: 10101603
[Apoptosis: molecular mechanisms]
L'apoptose: mecanismes moleculaires.
Solary E
Unite INSERM 517 Mort cellulaire et cancer, Facultes de Medecine et de Pharmacie, Dijon. esolary@u-bourgogne.fr
Comptes rendus des seances de la Societe de biologie et de ses filiales (FRANCE) 1998, 192 (6) p1065-76, ISSN 0037-9026 Journal Code: 7505439
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: FRENCH
Main Citation Owner: NLM
Record type: Completed
Apoptosis is a genetically programmed cell death that is required for morphogenesis during embryogenic development and for tissue homeostasis in adult organisms. In most cases, apoptosis involves cytochrome c release from mitochondria. In the cytosol, cytochrome c combines with APAF-1 in the presence of ATP to activate caspase -9 that, in turn, activates effectors caspases such as caspase -3. Bcl-2 and related proteins control cytochrome c release from the mitochondria whereas IAP (for Inhibitor of APoptosis) molecules modulate the activity of caspases . Plasma membrane receptors such as Fas (CD95, APO-1), characterized by a so-called "death domain" in their cytoplasmic domain, can activate the caspase cascade through adaptator molecules such as FADD (Fas-Associated protein with a Death Domain). Dysregulation of the apoptotic machinery plays a role in the pathogenesis of various diseases and molecules involved in cell death pathways are potential therapeutic targets in immunologic, neurologic, cancer , infectious and inflammatory diseases.

13/3,K,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10351714 99351182 PMID: 10422282
Targeted immunotherapy for malignant tumors]
Turuo T
Rinsho ketsueki The Japanese journal of clinical hematology (JAPAN) Jun 1999, 40 (6) p476-9, ISSN 0485-1439 Journal Code: 2984782R
Document type: Journal Article; Review; Review Literature
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed

Targeted immunotherapy for malignant tumors]
Jun 1999,
; Caspases--physiology--PH; Drug Resistance, Neoplasm; Tumor Cells, Cultured
Enzyme No.: EC 3.4.22.- (Caspases)
Chemical Name: Antineoplastic Agents; Immunotoxins; Quinolines; MS 209; Caspases

13/3,K,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10557716 20088209 PMID: 10624871

Tanshinone IIA isolated from Salvia miltiorrhiza BUNGE induced apoptosis in HL60 human premyelocytic leukemia cell line.

Yoon Y; Kim Y O; Jeon W K; Park H J; Sung H J

Laboratory of Cancer Research, Korea Institute of Oriental Medicine, Seoul, South Korea. ysyoon66@hanmail.net

Journal of ethnopharmacology (IRELAND) Dec 15 1999, 68 (1-3) p121-7, ISSN 0378-8741 Journal Code: 7903310

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Apoptosis is a new therapeutic target of cancer research. Tanshinone IIA isolated from Salvia miltiorrhiza BUNGE, a traditional oriental medical herb, was observed to induce apoptosis in HL60 human premyelocytic leukemia cell line. Tanshinone IIA induced DNA fragmentation into the multiples of 180 bp and increased the percentage of hypodiploid cells in flow cytometry after propidium iodide (PI) staining. Tanshinone IIA-induced apoptosis is accompanied by the specific proteolytic cleavage of poly(ADP-ribose) polymerase (PARP) and the activation of caspase -3, a major component in apoptotic cell death mechanism.

Dec 15 1999,

Apoptosis is a new therapeutic target of cancer research. Tanshinone IIA isolated from Salvia miltiorrhiza BUNGE, a traditional oriental medical herb, was observed...

13/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11047694 21034299 PMID: 11193041
The complexity of TNF-related apoptosis-inducing ligand.
Abe K; Kurakin A; Mohseni-Maybodi M; Kay B; Khosravi-Far R
Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, 99 Brookline Ave., RN 270F, Boston, MA 02215, USA.
Annals of the New York Academy of Sciences (United States) 2000, 926 p52-63, ISSN 0077-8923 Journal Code: 7506858
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
One of the major goals of researchers in the field of apoptosis is to understand the molecular mechanisms of the various components of the apoptotic pathways, with the hope to identify targets for novel cancer therapies. The discovery of a TNF-related, apoptosis-inducing ligand, TRAIL, that kills transformed cells with great specificity in vitro, has provided the hope that TRAIL may be used to induce cell death in tumor cells without affecting normal tissues. However, TRAIL signaling is very complex and a clear understanding of its function is necessary before it can be used in cancer therapy. Complexity of TRAIL-induced signaling is apparent from its ubiquitous expression, its ability to interact with five receptors, and its tumor-selective induction of apoptosis. The signaling events that mediate the tumor selectivity of TRAIL-induced apoptosis and the biological functions of each of the TRAIL receptors are not well characterized. This review will focus on the complexity of TRAIL and the role of c-FLIP in mediating TRAIL function.

```
 ds

Set     Items   Description
S1      33376   CASPASE??
S2    2471601   CANCER? OR TUMOR? OR MALIGNAN?
S3      12284   S1 AND S2
S4     709936   TARGET?
S5       1611   S3 AND S4
S6        654   TARGET?(5N)CASPASE??
S7        236   S6 AND S2
S8        134   S7 AND PY<=2000
S9         72   RD (unique items)
? s target? (5n) (cancer? or tumor? or malignan?)
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         1185785  CANCER?
         1518727  TUMOR?
          475787  MALIGNAN?
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           27083  S10
           33376  S1
     S11     265  S10 AND S1
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...examined 50 records  (150)
...examined 50 records  (200)
...examined 50 records  (250)
...completed examining records
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        37910018  PY<=2000
     S13      49  S12 AND PY<=2000
? t s13/3,k,ab/1-49

 13/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11106474   21122948   PMID: 11232194
  Apoptosis in hepatic pathophysiology.
  Patel T
  Division of Gastroenterology, Department of Medicine, Scott and White
Clinic, Texas A & M University System Health Sciences Center College of
Medicine, Temple, Texas, USA. tpatel@swmail.sw.org
  Clinics in liver disease (United States) May 2000, 4 (2)
 p295-317, ISSN 1089-3261 Journal Code: 9710002
  Contract/Grant No.: DK02678; DK; NIDDK
  Document type: Journal Article; Review; Review, Tutorial
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Apoptosis is a fundamental biologic process that is important in many
physiologic and pathophysiologic processes in the liver. Although
dysregulation of apoptosis may contribute to a wide range of diseases, the
role of this process in liver disease and pathophysiology has only recently
begun to be recognized and remains to be fully defined. Several important
questions remain unanswered: How does excessive apoptosis in response to
injury contribute to inflammation and fibrogenesis in the liver? How does
```

control of apoptosis contribute to the regulation of hepatic structure following injury? What is the role of death receptors in hepatic disease? Can an understanding of apoptosis be helpful in therapeutic modulation of specific liver diseases or liver cancer? The identification of target molecules involved in apoptosis raises the prospect of pharmacologic modulation that may result in better treatment options for patients with liver diseases. Inhibition of apoptosis is likely to be useful in treating fulminant hepatic failure or in organ preservation before transplantation. In these situations, treatment is for a limited period, and the potential hazards of nonselective long-term inhibition of apoptosis are minimized. Safe and organ-specific inhibitors of apoptosis would be required for prolonged treatment of chronic liver diseases. For treatment of liver tumors, the goal is to induce apoptosis selectively in cancer cells. Drugs that decrease the apoptotic threshold by modulating the intracellular regulatory mechanisms and drugs that enhance the susceptibility of cancer cells to undergo immune-mediated apoptosis will be useful in the treatment of liver cancers. The rapid advances in the understanding of the intracellular mechanisms and the regulation of apoptosis will ultimately result in a better understanding of the role of apoptosis in the pathophysiology of liver diseases and may allow therapeutic modulation of this process.

May 2000,

... an understanding of apoptosis be helpful in therapeutic modulation of specific liver diseases or liver cancer? The identification of target molecules involved in apoptosis raises the prospect of pharmacologic modulation that may result in better...

; Apoptosis--immunology--IM; Caspases--physiology--PH; Genes, bcl-2 --genetics--GE; Genes, bcl-2--physiology--PH; Growth Substances

```
      ---  -----  -----------
? s caspase? (5n) (conjugat? or link? or fus? or chimer?)
           40944  CASPASE?
          244412  CONJUGAT?
         1124033  LINK?
          484612  FUS?
           92086  CHIMER?
      S1     660  CASPASE? (5N) (CONJUGAT? OR LINK? OR FUS? OR CHIMER?)
? s antibod? or ligand or receptor
Processing
         1405474  ANTIBOD?
          339765  LIGAND
         1565538  RECEPTOR
      S2 2953390  ANTIBOD? OR LIGAND OR RECEPTOR
? s s1 and s2
             660  S1
         2953390  S2
      S3     269  S1 AND S2
? s fas
      S4   37293  FAS
? s s3 not s4
             269  S3
           37293  S4
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Processing
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 7/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

11913774   99357121   PMID: 10430052
  Intracellular CXCR4 signaling, neuronal apoptosis and neuropathogenic
mechanisms of HIV-1-associated dementia.
  Zheng J; Thylin M R; Ghorpade A; Xiong H; Persidsky Y; Cotter R; Niemann
D; Che M; Zeng Y C; Gelbard H A; Shepard R B; Swartz J M; Gendelman H E
  Department of Pathology, University of Nebraska Medical Center, Omaha
68198-5215, USA.
  Journal of neuroimmunology (NETHERLANDS) Aug 3 1999, 98 (2)
 p185-200, ISSN 0165-5728 Journal Code: 8109498
  Contract/Grant No.: 501 NS34239-02; NS; NINDS; P01 NS31492-01; NS; NINDS;
R01 NS34239-01; NS; NINDS; +
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The mechanism(s) by which HIV-1 affects neural injury in HIV-1-associated
dementia (HAD) remains unknown. To ascertain the role that cellular and
viral macrophage products play in HAD neurotoxicity, we explored one
potential route for neuronal demise, CXCR4. CXCR4, expressed on lymphocytes
and neurons, is both a part of neural development and a co-receptor
 for HIV-1. Its ligand , stromal cell-derived factor-1alpha
(SDF-1alpha), affects neuronal viability. GTP binding protein (G-protein)
```

linked signaling after neuronal exposure to SDF-1alpha, virus-infected monocyte-derived macrophage (MDM) secretory products, and virus was determined. In both human and rat neurons, CXCR4 was expressed at high levels. SDF-1alpha/beta was detected predominantly in astrocytes and at low levels in MDM. SDF-1beta/beta was expressed in HAD brain tissue and upregulated in astrocytes exposed to virus infected and/or immune activated MDM conditioned media (fluids). HIV-1-infected MDM secretions, virus and SDF-1beta induced a G inhibitory (Gi) protein-linked decrease in cyclic AMP (cAMP) and increase inositol 1,4, 5-trisphosphate (IP3) and intracellular calcium. Such effects were partially blocked by **antibodies** to CXCR4 or removal of virus from MDM fluids. Changes in G-protein-coupled signaling correlated, but were not directly **linked** , to increased neuronal synaptic transmission, **C**

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? set hi ;set hi
HILIGHT set on as ''
HILIGHT set on as ''
? b 155 55 scisearch 340
       08aug03 08:29:29 User231882 Session D1208.2
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     $0.21  Estimated cost this search
     $0.21  Estimated total session cost   0.216 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2003/Aug W1
         (c) format only 2003 The Dialog Corp.
*File 155: Medline has been reloaded and accession numbers have
changed.  Please see HELP NEWS 155.
  File  55:Biosis Previews(R)  1993-2003/Aug W1
         (c) 2003 BIOSIS
*File  55: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File  34:SciSearch(R) Cited Ref Sci  1990-2003/Aug W1
         (c) 2003 Inst for Sci Info
  File 434:SciSearch(R) Cited Ref Sci  1974-1989/Dec
         (c) 1998 Inst for Sci Info
  File 340:CLAIMS(R)/US Patent  1950-03/Aug 05
         (c) 2003 IFI/CLAIMS(R)
*File 340: The Claims U.S. Patent databases have been reloaded.
 HELP NEWS340 & HELP ALERTS340 for search, display & Alert info.

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         1124033  LINK?
           92086  CHIMER?
          484612  FUS?
      S2 1851303  CONJUGAT? OR LINK? OR CHIMER? OR FUS?
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           40944  S1
         1851303  S2
      S3    4270  S1 AND S2
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? s antibod? or target? or receptor?? or ligand??
Processing
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          786848  TARGET?
         1981038  RECEPTOR??
          496783  LIGAND??
      S4 4012947  ANTIBOD? OR TARGET? OR RECEPTOR?? OR LIGAND??
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         4012947  S4
      S5    2212  S3 AND S4
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? s s6 and s3
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        35717408  PY<2000
      S8     129  S7 AND PY<2000
? s s8 and py<2000
Processing
             129  S8
        35717408  PY<2000
      S9     129  S8 AND PY<2000
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...examined 50 records  (100)
...completed examining records
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? s caspase(w)3 or caspase(w)6
           37425  CASPASE
         9202885  3
           19860  CASPASE(W)3
           37425  CASPASE
         6194700  6
             807  CASPASE(W)6
     S11   20033  CASPASE(W)3 OR CASPASE(W)6
? s s10 and s11
              76  S10
           20033  S11
     S12      27  S10 AND S11
? t s12/3,k,ab/1-27

 12/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.
```

11913774 99357121 PMID: 10430052

Intracellular CXCR4 signaling, neuronal apoptosis and neuropathogenic mechanisms of HIV-1-associated dementia.

Zheng J; Thylin M R; Ghorpade A; Xiong H; Persidsky Y; Cotter R; Niemann D; Che M; Zeng Y C; Gelbard H A; Shepard R B; Swartz J M; Gendelman H E

Department of Pathology, University of Nebraska Medical Center, Omaha 68198-5215, USA.

Journal of neuroimmunology (NETHERLANDS) Aug 3 **1999**, 98 (2) p185-200, ISSN 0165-5728 Journal Code: 8109498

Contract/Grant No.: 501 NS34239-02; NS; NINDS; P01 NS31492-01; NS; NINDS; R01 NS34239-01; NS; NINDS; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The mechanism(s) by which HIV-1 affects neural injury in HIV-1-associated dementia (HAD) remains unknown. To ascertain the role that cellular and viral macrophage products play in HAD neurotoxicity, we explored one potential route for neuronal demise, CXCR4. CXCR4, expressed on lymphocytes and neurons, is both a part of neural development and a co-receptor for HIV-1. Its ligand, stromal cell-derived factor-1alpha (SDF-1alpha), affects neuronal viability. GTP binding protein (G-protein) **linked** signaling after neuronal exposure to SDF-1alpha, virus-infected monocyte-derived macrophage (MDM) secretory products, and virus was determined. In both human and rat neurons, CXCR4 was expressed at high levels. SDF-1alpha/beta was detected predominantly in astrocytes and at low levels in MDM.

SDF-1beta/beta was expressed in HAD brain tissue and upregulated in astrocytes exposed to virus infected and/or immune activated MDM conditioned media (fluids). HIV-1-infected MDM secretions, virus and SDF-1beta induced a G inhibitory (Gi) protein-**linked** decrease in cyclic AMP (cAMP) and increase inositol 1,4, 5-trisphosphate (IP3) and intracellular calcium. Such effects were partially blocked by **antibodies** to CXCR4 or removal of virus from MDM fluids. Changes in G-protein-coupled signaling correlated, but were not directly **linked**, to increased neuronal synaptic transmission, **Caspase 3** activation and apoptosis. These data, taken together, suggest that CXCR4-mediated signal transduction may be a potential mechanism for neuronal dysfunction during HAD.

Aug 3 **1999**,

... stromal cell-derived factor-1alpha (SDF-1alpha), affects neuronal viability. GTP binding protein (G-protein) **linked** signaling after neuronal exposure to SDF-1alpha, virus-infected monocyte-derived macrophage (MDM) secretory products...

... HIV-1-infected MDM secretions, virus and SDF-1beta induced a G inhibitory (Gi) protein-**linked** decrease in cyclic AMP (cAMP) and increase inositol 1,4, 5-trisphosphate (IP3) and intracellular calcium. Such effects were partially blocked by **antibodies** to CXCR4 or removal of virus from MDM fluids. Changes in G-protein-coupled signaling correlated, but were not directly **linked** , to increased neuronal synaptic transmission, **Caspase 3** activation and apoptosis. These data, taken together, suggest that CXCR4-mediated signal transduction may be...

12/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11869203 99310651 PMID: 10381525

Caspase -mediated proteolysis and activation of protein kinase Cdelta plays a central role in neutrophil apoptosis.

Khwaja A; Tatton L

Department of Haematology, University College London Medical School, London, UK. a.khwaja@ucl.ac.uk

Blood (UNITED STATES) Jul 1 **1999**, 94 (1) p291-301, ISSN 0006-4971 Journal Code: 7603509

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Neutrophils undergo constitutive apoptosis when aged ex vivo. Recent studies have indicated roles for Fas/CD95 and the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase system in this process. We have investigated the role of protein kinase C (PKC) in neutrophil death. We show that there is proteolysis and activation of the novel isoform PKCdelta in aged neutrophils and that this process is accelerated by the addition of an agonistic Fas **antibody** . PKCdelta proteolysis occurs before the onset of any detectable features of apoptosis and pharmacologic inhibition of this enzyme inhibits neutrophil apoptosis. PKCdelta cleavage and activation is dependent on **caspase** -8/FADD-like interleukin-1beta converting enzyme (FLICE)-mediated processing of **caspase**-3 /CPP32. Neutrophil survival is prolonged by the addition of broad spectrum (BD.fmk) or **caspase**-8 targeted (zIETD.fmk) peptide **caspase** inhibitors. Inhibition of PKCdelta does not prevent apoptosis triggered by factor withdrawal in immature hematopoietic cells, including normal human CD34(+) progenitors indicating that within a given lineage, the mechanisms of apoptosis may be differentiation-stage-specific. Ex vivo aging of neutrophils leads to the increasing production of reactive oxygen species

and this is attenuated in cells treated with either **caspase** or PKCdelta inhibitors. Proteolytically activated PKCdelta acts as a molecular **link** between the Fas/CD95 receptor and the NADPH-oxidase system and plays a central role in regulating the process of neutrophil apoptosis.

Caspase -mediated proteolysis and activation of protein kinase Cdelta plays a central role in neutrophil apoptosis.
Jul 1 **1999**,
... aged neutrophils and that this process is accelerated by the addition of an agonistic Fas **antibody**. PKCdelta proteolysis occurs before the onset of any detectable features of apoptosis and pharmacologic inhibition of this enzyme inhibits neutrophil apoptosis. PKCdelta cleavage and activation is dependent on **caspase** -8/FADD-like interleukin-1beta converting enzyme (FLICE)-mediated processing of **caspase-3** /CPP32. Neutrophil survival is prolonged by the addition of broad spectrum (BD.fmk) or **caspase**-8 targeted (zIETD.fmk) peptide **caspase** inhibitors. Inhibition of PKCdelta does not prevent apoptosis triggered by factor withdrawal in immature hematopoietic...

... increasing production of reactive oxygen species and this is attenuated in cells treated with either **caspase** or PKCdelta inhibitors. Proteolytically activated PKCdelta acts as a molecular **link** between the Fas/CD95 receptor and the NADPH-oxidase system and plays a central role ...
Descriptors: Apoptosis; ***Caspases**--metabolism--ME; *Isoenzymes --metabolism--ME; *Neutrophils--pathology--PA; *Protein Kinase C --metabolism--ME
...Enzyme No.: 1.37 (Protein Kinase C); EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**); EC 3.4.22.- (**caspase** 8)
Chemical Name: Annexin V; Isoenzymes; protein kinase C-delta; Protein Kinase C; CPP32 protein; **Caspases**; **caspase 8**

12/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11855441 99296494 PMID: 10366428
Fas antigen modulates ultraviolet B-induced apoptosis of SVHK cells: sequential activation of **caspases** 8, 3, and 1 in the apoptotic process.
Takahashi H; Nakamura S; Asano K; Kinouchi M; Ishida-Yamamoto A; Iizuka H
Department of Dermatology, Asahikawa Medical College, Asahikawa, Japan. ht@asahikawa-med.ac.jp
Experimental cell research (UNITED STATES) Jun 15 **1999**, 249 (2) p291-8, ISSN 0014-4827 Journal Code: 0373226
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Interferon-gamma (IFN-gamma) induces various apoptosis-related proteins, including Fas antigen (Fas) in keratinocytes. Ultraviolet B (UVB) irradiation produces "sunburn cells," a specific type of apoptosis. Previously, we reported that IFN-gamma augments Fas-dependent apoptosis of SV40-transformed human keratinocytes (SVHK cells). **Caspases** are a new class of cysteine proteinases that play an important role in apoptosis. We investigated the mechanism of UVB-induced apoptosis by examining activation of the **caspase** cascade. UVB irradiation of SVHK cells increased the activities of **caspases** 1, 3, and 8, which were detected at 3 h, and peak activities occurred at 6 h. Pretreatment of SVHK cells with IFN-gamma significantly increased the activity of **caspases** 1, 3, and 8. UVB-induced **caspase** 8 stimulation was significantly suppressed only by **caspase** 8 inhibitor, while inhibitors of **caspases** 1, 3, and 8 significantly suppressed UVB-induced **caspase** 1 stimulation.

Caspase 3 and 8 inhibitors, but not **caspase** 1 inhibitor, significantly suppressed UVB-induced **caspase** 3 activity, suggesting sequential activation of **caspases** 8, 3, and 1 in UVB-irradiated SVHK cells. Cross-**linking** and immunoprecipitation analyses showed multimerization of Fas antigen following UVB irradiation of SVHK cells. Pretreatment of SVHK cells with IFN-gamma significantly augmented UVB-induced apoptosis that was accompanied by increased Fas expression. The susceptibility to UVB-induced apoptosis was also increased in Fas-transfected SVHK cells (F2 cells). Neutralizing anti-Fas **antibody** significantly suppressed **caspase** activation and Fas-dependent apoptosis of SVHK cells and F2 cells. In contrast, UVB-induced **caspase** activation and apoptosis were not inhibited by neutralizing anti-Fas **antibody** in both cell lines. Our results suggest that UVB directly activates Fas and subsequent **caspase** cascade resulting in apoptosis of SVHK cells. Furthermore, the expression level of Fas antigen in keratinocytes influenced their susceptibility to UVB-induced apoptosis. Copyright 1999 Academic Press.

Fas antigen modulates ultraviolet B-induced apoptosis of SVHK cells: sequential activation of **caspases** 8, 3, and 1 in the apoptotic process.
Jun 15 **1999**,
... reported that IFN-gamma augments Fas-dependent apoptosis of SV40-transformed human keratinocytes (SVHK cells). **Caspases** are a new class of cysteine proteinases that play an important role in apoptosis. We investigated the mechanism of UVB-induced apoptosis by examining activation of the **caspase** cascade. UVB irradiation of SVHK cells increased the activities of **caspases** 1, 3, and 8, which were detected at 3 h, and peak activities occurred at 6 h. Pretreatment of SVHK cells with IFN-gamma significantly increased the activity of **caspases** 1, 3, and 8. UVB-induced **caspase** 8 stimulation was significantly suppressed only by **caspase** 8 inhibitor, while inhibitors of **caspases** 1, 3, and 8 significantly suppressed UVB-induced **caspase** 1 stimulation. **Caspase** 3 and 8 inhibitors, but not **caspase** 1 inhibitor, significantly suppressed UVB-induced **caspase** 3 activity, suggesting sequential activation of **caspases** 8, 3, and 1 in UVB-irradiated SVHK cells. Cross-**linking** and immunoprecipitation analyses showed multimerization of Fas antigen following UVB irradiation of SVHK cells. Pretreatment...

... induced apoptosis was also increased in Fas-transfected SVHK cells (F2 cells). Neutralizing anti-Fas **antibody** significantly suppressed **caspase** activation and Fas-dependent apoptosis of SVHK cells and F2 cells. In contrast, UVB-induced **caspase** activation and apoptosis were not inhibited by neutralizing anti-Fas **antibody** in both cell lines. Our results suggest that UVB directly activates Fas and subsequent **caspase** cascade resulting in apoptosis of SVHK cells. Furthermore, the expression level of Fas antigen in...
Descriptors: Antigens, CD95--physiology--PH; *Apoptosis --radiation effects--RE; ***Caspase** 1--metabolism--ME; ***Caspases**--metabolism --ME; *Keratinocytes--enzymology--EN; *Keratinocytes--radiation effects --RE; *Ultraviolet Rays; Antigens, CD95--biosynthesis--BI; Antigens, CD95 --immunology--IM; Antigens, CD95--metabolism--ME; **Caspase** 1 --antagonists and inhibitors--AI; **Caspase** 1--radiation effects--RE; **Caspases**--antagonists and inhibitors--AI; **Caspases**--radiation effects--RE; Cell Line; Enzyme Activation--radiation effects--RE; Immune Sera--pharmacology--PD
Enzyme No.: EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**) ; EC 3.4.22.- (**caspase** 8); EC 3.4.22.36 (**Caspase** 1)
Chemical Name: Antigens, CD95; Immune Sera; CPP32 protein; **Caspases** ; **caspase 8**; **Caspase** 1

12/3,K,AB/4 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11847277 99288074 PMID: 10358162
Protection against CD95-mediated apoptosis by inorganic mercury in Jurkat T cells.
Whitekus M J; Santini R P; Rosenspire A J; McCabe M J
Institute of Chemical Toxicology, Detroit, MI 48201, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Jun 15 **1999**, 162 (12) p7162-70, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: P30 ES06639; ES; NIEHS; R29 ES07365; ES; NIEHS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Dysregulation of CD95/Fas-mediated apoptosis has been implicated as a contributing factor in autoimmune disorders. Animal studies clearly have established a connection between mercury exposure and autoimmune disease in rodents, while case reports have suggested a **link** between accidental mercury contamination and autoimmune disease in humans. The mechanism(s) for these associations are poorly understood. Using the Jurkat cell model, we have found that low levels (</=10 &mgr;M) of inorganic mercury (i.e., HgCl2) attenuated anti-CD95-mediated growth arrest and markedly enhanced cell survival. Several biochemical assays for apoptosis, including DNA degradation, poly(ADP-ribose) polymerase degradation, and phosphatidylserine externalization, directly verified that HgCl2 attenuated anti-CD95-mediated apoptosis. In an attempt to further characterize the effect of mercury on CD95-mediated apoptosis, several signaling components of the CD95 death pathway were analyzed to determine whether HgCl2 could modulate them. HgCl2 did not modulate CD95 expression; however, it did block CD95-induced **caspase-3** activation. HgCl2 was not able to attenuate TNF-alpha-mediated apoptosis in U-937 cells, or ceramide-C6-mediated apoptosis in Jurkat cells, suggesting that mercury acts upstream of, or does not involve, these signals. Thus, inorganic mercury specifically attenuates CD95-mediated apoptosis likely by targeting a signaling component that is upstream of **caspase-3** activation and downstream of CD95.

Jun 15 **1999**,
...connection between mercury exposure and autoimmune disease in rodents, while case reports have suggested a **link** between accidental mercury contamination and autoimmune disease in humans. The mechanism(s) for these associations...

...could modulate them. HgCl2 did not modulate CD95 expression; however, it did block CD95-induced **caspase-3** activation. HgCl2 was not able to attenuate TNF-alpha-mediated apoptosis in U-937 cells...

... specifically attenuates CD95-mediated apoptosis likely by targeting a signaling component that is upstream of **caspase-3** activation and downstream of CD95.
; **Antibodies**, Monoclonal--metabolism--ME; **Antibodies**, Monoclonal--pharmacology--PD; Antigens, CD95--immunology--IM; Antigens, CD95--metabolism--ME; Binding Sites, **Antibody**--drug effects--DE; Binding Sites, **Antibody**--immunology--IM; **Caspases**--metabolism --ME; Cell Death--drug effects--DE; Cell Death--immunology--IM; Cell Division--drug effects...
Enzyme No.: EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**)

Chemical Name: **Antibodies**, Monoclonal; Antigens, CD95; Binding Sites, **Antibody**; Ceramides; Growth Inhibitors; Tumor Necrosis Factor; Mercury; CPP32 protein; **Caspases**

12/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11801700 99240876 PMID: 10222310
Inhibition of Fas receptor (CD95)-induced hepatic **caspase** activation and apoptosis by acetaminophen in mice.
Lawson J A; Fisher M A; Simmons C A; Farhood A; Jaeschke H
Department of Pharmacology, Pharmacia & Upjohn, Inc., Kalamazoo, Michigan 49007, USA.
Toxicology and applied pharmacology (UNITED STATES) May 1 **1999**, 156 (3) p179-86, ISSN 0041-008X Journal Code: 0416575
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mechanism of liver cell injury induced by an overdose of the analgesic acetaminophen (AAP) remains controversial. Recently, it was hypothesized that a significant number of hepatocytes die by apoptosis. Since **caspases** have been implicated as critical signal and effector proteases in apoptosis, we investigated their potential role in the pathophysiology of AAP-induced liver injury. Male C3Heb/FeJ mice were fasted overnight and then treated with 500 mg/kg AAP. Liver injury became apparent at 4 h and was more severe at 6 h (plasma ALT activities: 4110 +/- 320 U/liter; centrilobular necrosis). DNA fragmentation increased parallel to the increase of plasma ALT values. At 6 h there was a 420% increase of DNA fragmentation and a 74-fold increase of terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL)-positive cells located predominantly around central veins. However, the activity of the proapoptotic **caspase-3** was not increased at any time after AAP. In contrast, injection of the anti-Fas **antibody** Jo-2 (positive control) caused a 28-fold increase of **caspase-3** activity and severe DNA fragmentation before significant ALT release. Treatment with the **caspase** inhibitor ZVAD-CHF2 had no effect on AAP toxicity but completely prevented Jo-mediated apoptosis. In contrast, Jo-induced **caspase** activation and apoptosis could be inhibited by AAP treatment in a time- and dose-dependent manner. We conclude that AAP-induced DNA fragmentation does not involve **caspases** , suggesting a direct activation of endonucleases through elevated Ca2+ levels. In addition, electrophilic metabolites of AAP may inactivate **caspases** or their activation pathway. This indicates that AAP metabolism has the potential to inhibit signal transduction mechanisms of receptor-mediated apoptosis.

Inhibition of Fas receptor (CD95)-induced hepatic **caspase** activation and apoptosis by acetaminophen in mice.
May 1 **1999**,
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inactivate **caspases** or their activation pathway. This indicates that AAP metabolism has the potential to inhibit signal...
...Descriptors: toxicity--TO; *Analgesics, Non-Narcotic--toxicity--TO; *Antigens, CD95--physiology--PH; *Apoptosis--drug effects--DE; * **Caspases**--metabolism--ME; *Liver--drug effects--DE...; metabolism--ME ; Blotting, Western; DNA Fragmentation--drug effects--DE; Enzyme Activation --drug effects--DE; Enzyme-**Linked** Immunosorbent Assay; Imines --metabolism--ME; In Situ Nick-End Labeling; Liver--enzymology--EN; Mice; Mice...
Enzyme No.: EC 3.4.22.- (**Caspases**)
Chemical Name: Analgesics, Non-Narcotic; Antigens, CD95; Benzoquinones; Imines; Acetaminophen; N-acetyl-4-benzoquinoneimine; **Caspases**

12/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11800814 99239953 PMID: 10225447
Blockade of the Fas-triggered intracellular signaling pathway in human melanomas is circumvented by cytotoxic lymphocytes.
Ferrarini M; Imro M A; Sciorati C; Heltai S; Protti M P; Pellicciari C; Rovere P; Manfredi A A; Rugarli C
Laboratorio di Immunologia dei Tumori, Divisione di Medicina II, H San Raffaele Scientific Institute, Milan, Italy. ferrarini.m@hsr.it
International journal of cancer. Journal international du cancer (UNITED STATES) May 17 **1999**, 81 (4) p573-9, ISSN 0020-7136
Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Fas and Fas ligand (FasL) have been found both in lymphoid and in non-lymphoid malignancies, and are thought to play a role in the interplay between tumors and the immune system. Here we investigated Fas/FasL expression, function and intracellular signalling pathways in human melanomas. Of 5 melanoma cell lines, 3 expressed Fas at their surface, and all of them expressed FasL. FasL was functional, since it triggered Fas-induced apoptosis of human T lymphocytes clones. Conversely, cross-**linking** of Fas molecule with a specific monoclonal **antibody** failed to induce apoptosis in any of the melanomas tested, or ceramide intracellular accumulation or **caspase-3** activation, pointing to an early alteration in the Fas-triggered signaling cascade. All melanomas retained the ability to undergo apoptosis induced by cytotoxic lymphocytes, which was mediated by the granule exocytosis mechanism. This suggests that melanoma cells evade immune-mediated Fas-triggered apoptosis via a selective blockade of the Fas apoptotic pathway. Cytotoxic lymphocytes, however, may circumvent tumor resistance to Fas-induced death via granzyme-mediated apoptosis, further supporting the development of immunotherapeutic strategies in the treatment of cancer.

May 17 **1999**,
... was functional, since it triggered Fas-induced apoptosis of human T lymphocytes clones. Conversely, cross-**linking** of Fas molecule with a specific monoclonal **antibody** failed to induce apoptosis in any of the melanomas tested, or ceramide intracellular accumulation or **caspase-3** activation, pointing to an early alteration in the Fas-triggered signaling cascade. All melanomas retained...

12/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11795241 99234224 PMID: 10215653

Proteasome inhibition leads to significant reduction of Bcr-Abl expression and subsequent induction of apoptosis in K562 human chronic myelogenous leukemia cells.

Dou Q P; McGuire T F; Peng Y; An B

Drug Discovery Program, H. Lee Moffitt Cancer Center and Research Institute, Department of Biochemistry, College of Medicine, University of South Florida, Tampa, Florida, USA. douqp@moffitt.usf.edu

Journal of pharmacology and experimental therapeutics (UNITED STATES) May **1999**, 289 (2) p781-90, ISSN 0022-3565 Journal Code: 0376362

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The **chimeric** oncogene bcr-abl is detected in virtually every case of chronic myelogenous leukemia. It has been shown that cells (such as K562) expressing Bcr-Abl/p210, a protein tyrosine kinase, not only undergo cellular transformation but also demonstrate multiple drug resistance. Recent studies also demonstrate that the proteasome is involved in the survival signaling pathway(s). In the current study, we tested the hypothesis that the proteasome might play a role in regulating Bcr-Abl function. We have demonstrated by using a variety of inhibitors that inhibition of the proteasome, but not of the cysteine protease, activity is able to activate the apoptotic cell death program in K562 cells. Proteasome inhibition-induced apoptosis is demonstrated by condensation and fragmentation of nuclei, appearance of an apoptotic population with sub-G1 DNA content, the internucleosomal fragmentation of DNA, and cleavage of poly(ADP-ribose) polymerase, and can be blocked by a specific **caspase -3**-like tetrapeptide inhibitor. Western blot analysis with specific **antibodies** to c-Abl and Bcr proteins show that treatment of K562 cells with a proteasome inhibitor results in significant reduction of Bcr-Abl protein expression, which occurs several hours before the onset of apoptotic execution. Levels of c-Abl/p145 and Bcr/p160 proteins, however, remain essentially unaltered at that time. Furthermore, reduced Bcr-Abl expression is reflected in significantly attenuated Bcr-Abl-mediated protein tyrosine phosphorylation. Taken together, these results indicate that proteasome inhibition is sufficient to inactivate Bcr-Abl function and subsequently activate the apoptotic death program in cells that are resistant to apoptosis induced by chemotherapy.

May **1999**,

The **chimeric** oncogene bcr-abl is detected in virtually every case of chronic myelogenous leukemia. It has...

... DNA, and cleavage of poly(ADP-ribose) polymerase, and can be blocked by a specific **caspase-3**-like tetrapeptide inhibitor. Western blot analysis with specific **antibodies** to c-Abl and Bcr proteins show that treatment of K562 cells with a proteasome...

Descriptors: Apoptosis; *Cysteine Endopeptidases--metabolism--ME; *Cysteine Proteinase Inhibitors--pharmacology--PD; ***Fusion** Proteins, bcr-abl--biosynthesis--BI; *Leukemia, Myeloid, Chronic--pathology--PA; *Multienzyme Complexes--metabolism--ME; Blotting, Western; **Caspases** --metabolism--ME; **Caspases**--physiology--PH; Cell Nucleus --ultrastructure--UL; DNA Fragmentation; Enzyme Activation--physiology--PH; Flow Cytometry; Leupeptins...

...Enzyme No.: 1.112 (Protein-Tyrosine Kinase); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.22.- (**Caspases**); EC 3.4.99.46 (multicatalytic endopeptidase complex)

Chemical Name: Cysteine Proteinase Inhibitors; **Fusion** Proteins, bcr-abl; Leupeptins; Multienzyme Complexes; carbobenzoxy-leucyl-leucyl-norvalinal; Protein-Tyrosine Kinase; Cysteine Endopeptidases; **Caspases**; multicatalytic endopeptidase complex

12/3,K,AB/8 (Item 8 from file: 155)

11739362 99176432 PMID: 10078546

Essential role of **caspase-3** in apoptosis of mouse beta-cells transfected with human Fas.

Yamada K; Ichikawa F; Ishiyama-Shigemoto S; Yuan X; Nonaka K
Department of Medicine, Kurume University School of Medicine, Japan. yamada@med.kurume-u.ac.jp

Diabetes (UNITED STATES) Mar **1999**, 48 (3) p478-83, ISSN 0012-1797 Journal Code: 0372763
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Several recent studies have indicated that the Fas-Fas ligand system may be critical for pancreatic beta-cell destruction in type 1 diabetes. Although the fundamental roles of **caspases** in the mammalian apoptotic machinery have been elucidated, it is not known which **caspase** or **caspases** play a major role in Fas-mediated apoptosis of beta-cells. In this study, we transfected human Fas cDNA into a mouse beta-cell line (betaTC1) and established a beta-cell clone expressing human Fas. This clone, designated hFas/betaTC1, underwent apoptosis when exposed to anti-Fas, showing hallmarks of apoptosis (chromatin condensation, nucleolar disintegration, internucleosomal DNA fragmentation, and annexin V staining), indicating that the mouse beta-cell line has the intact machinery of Fas-mediated apoptosis. The cross-**linking** of Fas by anti-Fas resulted in the elevation of **caspase-3**-like, but not **caspase** -1-like, protease activity 2-12 h after the addition of the anti-Fas. A **caspase-3** inhibitor, Z-Asp-Glu-Val-Asp-fluoromethyl ketone, attenuated the Fas-mediated beta-cell apoptosis, while a **caspase** -1 inhibitor, acetyl-Tyr-Val-Ala-Asp-chloromethylketone, failed to suppress the apoptosis. Thus the Fas-induced death signal apparently bypassed **caspase**-1 in the cells. Furthermore, an antisense **caspase-3** construct blocked **caspase-3** activation and substantially suppressed Fas-triggered apoptosis of hFas/betaTC1 cells. These observations suggest the essential role of **caspase-3** in Fas-mediated apoptosis of the beta-cell line.

Essential role of **caspase-3** in apoptosis of mouse beta-cells transfected with human Fas.
Mar **1999**,
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... the mouse beta-cell line has the intact machinery of Fas-mediated apoptosis. The cross-**linking** of Fas by anti-Fas resulted in the elevation of **caspase-3**-like, but not **caspase**-1-like, protease activity 2-12 h after the addition of the anti-Fas. A **caspase-3** inhibitor, Z-Asp-Glu-Val-Asp-fluoromethyl ketone, attenuated the Fas-mediated beta-cell apoptosis, while a **caspase**-1 inhibitor, acetyl-Tyr-Val-Ala-Asp-chloromethylketone, failed to suppress the apoptosis. Thus the Fas-induced death signal apparently bypassed **caspase**-1 in the cells. Furthermore, an antisense **caspase-3** construct blocked **caspase-3** activation and substantially suppressed Fas-triggered apoptosis of hFas/betaTC1 cells. These observations suggest the essential role of **caspase-3** in Fas-mediated apoptosis of the beta-cell line.

Descriptors: Antigens, CD95--physiology--PH; *Apoptosis--physiology--PH; ***Caspases**--metabolism--ME; *Cysteine Proteinase Inhibitors --pharmacology--PD; Amino Acid Chloromethyl Ketones--pharmacology--PD;

Antibodies--pharmacology--PD; Antigens, CD95--genetics--GE; Apoptosis --drug effects--DE; Cell Survival--drug effects--DE...
Enzyme No.: EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**)

Chemical Name: Amino Acid Chloromethyl Ketones; **Antibodies**; Antigens, CD95; Cysteine Proteinase Inhibitors; DNA, Complementary; N-acetyl-tyrosyl-valyl-alanyl-aspartyl chloromethyl ketone; Oligopeptides; Recombinant Proteins; benzoylcarbonyl-aspartyl-glutamyl-valyl-aspartyl-fluo romethyl ketone; CPP32 protein; **Caspases**

12/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11621452 99054652 PMID: 9840917
Inhibition of Fas-induced apoptosis by Bcl-2.
Kawahara A; Kobayashi T; Nagata S
Osaka Bioscience Institute, Suita, Japan.
Oncogene (ENGLAND) Nov 19 **1998**, 17 (20) p2549-54, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Jurkat cells express Fas, and rapidly undergo apoptosis in response to Fas ligand or an agonistic anti-Fas **antibody**. This apoptotic pathway is mediated by a cascade of **caspases**. In this report, we show that Fas activation induced the processing of **caspase** 8 in Jurkat cells with a time frame similar to the activation of **caspase 3** and the proteolysis of nuclear proteins. Jurkat cell transformants that overexpress Bcl-2 were partially but not completely resistant to the Fas-induced apoptosis. Little processing of **caspase** 8 was observed upon Fas activation in these transformants. Furthermore, although **caspase** 8 was recruited to Fas upon Fas activation in the parental Jurkat cells, the recruitment of **caspase** 8 to Fas was inhibited in the transformants overexpressing Bcl-2. These results suggest that Bcl-2 inhibits Fas-induced apoptosis by preventing the formation of the death-inducing signaling complex that is composed of Fas, FADD/MORT1, and **caspase** 8.

Nov 19 **1998**,
... Fas, and rapidly undergo apoptosis in response to Fas ligand or an agonistic anti-Fas **antibody**. This apoptotic pathway is mediated by a cascade of **caspases** . In this report, we show that Fas activation induced the processing of **caspase** 8 in Jurkat cells with a time frame similar to the activation of **caspase 3** and the proteolysis of nuclear proteins. Jurkat cell transformants that overexpress Bcl-2 were partially but not completely resistant to the Fas-induced apoptosis. Little processing of **caspase** 8 was observed upon Fas activation in these transformants. Furthermore, although **caspase** 8 was recruited to Fas upon Fas activation in the parental Jurkat cells, the recruitment of **caspase** 8 to Fas was inhibited in the transformants overexpressing Bcl-2. These results suggest that...

... formation of the death-inducing signaling complex that is composed of Fas, FADD/MORT1, and **caspase** 8.
; Antigens, CD95--physiology--PH; Biological Transport; **Caspases** --metabolism--ME; Enzyme Activation; Enzyme Precursors--metabolism--ME; Genes, bcl-2; Jurkat Cells; Macromolecular Systems...

...Glycoproteins--physiology--PH; Mice; Neoplasm Proteins--antagonists and inhibitors--AI; Neoplasm Proteins--metabolism--ME; Recombinant **Fusion** Proteins--physiology--PH; Transfection

Enzyme No.: EC 3.4.22.- (**Caspases**); EC 3.4.22.- (**caspase** 8)
...Chemical Name: FasL protein; Macromolecular Systems; Membrane Glycoproteins; Neoplasm Proteins; Proto-Oncogene Proteins c-bcl-2; Recombinant **Fusion** Proteins; **Caspases**; **caspase 8**

12/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11614659 99047701 PMID: 9830064
TRAIL/Apo2L activates c-Jun NH2-terminal kinase (JNK) via **caspase** -dependent and **caspase**-independent pathways.
Muhlenbeck F; Haas E; Schwenzer R; Schubert G; Grell M; Smith C; Scheurich P; Wajant H
Institute of Cell Biology and Immunology, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany.
Journal of biological chemistry (UNITED STATES) Dec 4 **1998**, 273 (49) p33091-8, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In this study we show that TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), also called Apo2L, activates the c-Jun N-terminal kinase (JNK). Interestingly, TRAIL-induced JNK activation occurs in a cell type-specific manner. In HeLa cells, TRAIL-induced JNK activation can be completely blocked with the cysteine protease inhibitor zVAD-fmk, whereas the same inhibitor has no, or even a stimulatory, effect on JNK activation in Kym-1 cells. Hence, TRAIL can engage at least two independent pathways leading to JNK activation, one that is cysteine protease-dependent and one that is cysteine protease-independent. To investigate whether the cysteine protease-dependent signaling of TRAIL leading to JNK activation is related to the apoptotic pathway engaged by this ligand, we investigated HeLa cells stably overexpressing a dominant negative mutant of FADD (Fas-associating protein with death domain) (GFP(green fluorescent protein)DeltaFADD). In these cells, TRAIL-induced cell death and activation of the apoptosis executioner **caspase**-8 (FLICE/MACH) and **caspase** -**3** (YAMA, CPP-32, Apopain), that belong to **caspase** subfamily of cysteine proteases, were abrogated, whereas JNK activation remained unaffected and was still sensitive toward z-VAD-fmk. Similar data were found in HeLa cells overexpressing Apo1/Fas and GFPDeltaFADD upon stimulation with agonistic **antibodies**. These data suggest that cross-**linking** of the TRAIL receptors and Apo1/Fas, respectively, engages a FADD-dependent pathway leading to the activation of apoptotic **caspases** and, in parallel, a FADD-independent pathway leading to the stimulation of one or more cysteine proteases capable to activate JNK but not sufficient for the induction of cell death.

TRAIL/Apo2L activates c-Jun NH2-terminal kinase (JNK) via **caspase** -dependent and **caspase**-independent pathways.
Dec 4 **1998**,
... protein)DeltaFADD). In these cells, TRAIL-induced cell death and activation of the apoptosis executioner **caspase**-8 (FLICE/MACH) and **caspase-3** (YAMA, CPP-32, Apopain), that belong to **caspase** subfamily of cysteine proteases, were abrogated, whereas JNK activation remained unaffected and was still sensitive...

... data were found in HeLa cells overexpressing Apo1/Fas and GFPDeltaFADD upon stimulation with agonistic **antibodies**. These data suggest that cross-**linking** of the TRAIL receptors and Apo1/Fas, respectively, engages a FADD-dependent pathway leading to the activation of apoptotic **caspases** and, in parallel, a FADD-independent pathway leading to the

stimulation of one or more...
Descriptors: Ca(2+)-Calmodulin Dependent Protein Kinase--metabolism--ME; ***Caspases**--metabolism--ME; *Membrane Glycoproteins--metabolism--ME; *Tumor Necrosis Factor--metabolism--ME
...Enzyme No.: c-Jun amino-terminal kinase); EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**)
...Chemical Name: Necrosis Factor; Ca(2+)-Calmodulin Dependent Protein Kinase; c-Jun amino-terminal kinase; CPP32 protein; **Caspases**

12/3,K,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11589043 99021382 PMID: 9806545
PML is essential for multiple apoptotic pathways.
Wang Z G; Ruggero D; Ronchetti S; Zhong S; Gaboli M; Rivi R; Pandolfi P P
Department of Human Genetics and Molecular Biology Program, Memorial Sloan-Kettering Cancer Center, Graduate School of Medical Sciences, Cornell University, New York, New York 10021, USA.
Nature genetics (UNITED STATES) Nov **1998**, 20 (3) p266-72, ISSN 1061-4036 Journal Code: 9216904
Contract/Grant No.: CA 71692; CA; NCI; CA-08748; CA; NCI
Comment in Nat Genet. 1998 Nov;20(3) 220-2; Comment in PMID 9806533
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The PML gene of acute promyelocytic leukaemia (APL) encodes a cell growth and tumour suppressor, however, the mechanisms by which PML suppresses tumorigenesis are poorly understood. We show here that Pml is required for Fas- and **caspase** -dependent DNA-damage-induced apoptosis. We also found that Pml is essential for induction of programmed cell death by Fas, tumour necrosis factor alpha (TNF), ceramide and type I and II interferons (IFNs). As a result, Pml-/- mice and cells are protected from the lethal effects of ionizing radiation and anti-Fas **antibody**. Pml is required for **caspase** 1 and **caspase 3** activation upon exposure to these stimuli. The PML-RAR alpha **fusion** protein of APL renders haemopoietic progenitor cells resistant to Fas-, TNF- and IFN-induced apoptosis with a lack of **caspase 3** activation, thus acting as a Pml dominant-negative product. These results demonstrate that Pml is a mediator of multiple apoptotic signals, and implicate inhibition of apoptosis in the pathogenesis of APL.

Nov **1998**,
... suppresses tumorigenesis are poorly understood. We show here that Pml is required for Fas- and **caspase** -dependent DNA-damage-induced apoptosis. We also found that Pml is essential for induction of...

... mice and cells are protected from the lethal effects of ionizing radiation and anti-Fas **antibody**. Pml is required for **caspase** 1 and **caspase 3** activation upon exposure to these stimuli. The PML-RAR alpha **fusion** protein of APL renders haemopoietic progenitor cells resistant to Fas-, TNF- and IFN-induced apoptosis with a lack of **caspase 3** activation, thus acting as a Pml dominant-negative product. These results demonstrate that Pml is...
; Antigens, CD95--physiology--PH; Apoptosis--drug effects--DE; Apoptosis --genetics--GE; **Caspases**--physiology--PH; Ceramides--pharmacology--PD ; DNA Damage; Enzyme Activation; Interferons--pharmacology--PD; Leukemia, Promyelocytic, Acute...

...ET; Leukemia, Promyelocytic, Acute--genetics--GE; Mice; Mice, Knockout; Neoplasm Proteins--genetics--GE; Oncogene Proteins, **Fusion**--genetics --GE; Oncogene Proteins, **Fusion**--physiology--PH; Transcription

Factors--genetics--GE; Tumor Necrosis Factor--pharmacology--PD
Enzyme No.: EC 3.4.22.- (**Caspases**)
Chemical Name: Antigens, CD95; Ceramides; Neoplasm Proteins; Oncogene Proteins, **Fusion**; PML-RARalpha protein; Transcription Factors; Tumor Necrosis Factor; transcription factor PML; Interferons; **Caspases**

12/3,K,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11555729 98447653 PMID: 9774422
Identification of apoptosis-associated proteins in a human Burkitt lymphoma cell line. Cleavage of heterogeneous nuclear ribonucleoprotein A1 by **caspase 3**.
Brockstedt E; Rickers A; Kostka S; Laubersheimer A; Dorken B; Wittmann-Liebold B; Bommert K; Otto A
Proteinchemie, D-13125 Berlin, Germany.
Journal of biological chemistry (UNITED STATES) Oct 23 **1998**, 273 (43) p28057-64, ISSN 0021-9258 Journal Code: 2985121R
Erratum in J Biol Chem 1998 Dec 11;273(50) 33884
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Apoptosis or programmed cell death is essential in the process of controlling lymphocyte growth and selection. We identified proteins that are involved in anti-IgM **antibody**-mediated apoptosis using a subclone of the human Burkitt lymphoma cell line BL60. Apoptosis-associated proteins were detected by high resolution two-dimensional gel electrophoresis on a micropreparative scale. Comparison of the high resolution two-dimensional gel electrophoresis protein patterns from apoptotic and non-apoptotic cells showed differences in approximately 80 spots including protein modifications. Analysis of the predominantly altered proteins was performed by internal Edman microsequencing and/or by peptide mass fingerprinting using matrix-assisted laser desorption/ionization mass spectrometry. Analysis was significantly improved by using new micropreparative high resolution two-dimensional gels employing high protein concentrations. The following 12 apoptosis-associated proteins were identified: heterogeneous nuclear ribonucleoprotein (hnRNP) A1, hnRNP C1/C2, **FUSE**-binding protein, dUTPase, lymphocyte-specific protein LSP1, UV excision repair protein RAD23 homologue B (HHR23B), 60 S acidic ribosomal protein P0 (L10E), heterochromatin protein 1 homologue alpha (HP1alpha), nucleolin, lamin, neutral calponin, and actin. Fragmentation of actin, hnRNP A1, hnRNP C1/C2, 60 S acidic ribosomal protein P0, lamin, and nucleolin could be inhibited by benzyloxycarbonyl-Asp(OMe)-Glu(OMe)-Val-Asp(OMe)-fluoromethyl ketone, a selective irreversible inhibitor of CPP32 (**caspase 3**).

... proteins in a human Burkitt lymphoma cell line. Cleavage of heterogeneous nuclear ribonucleoprotein A1 by **caspase 3**.
Oct 23 **1998**,
...of controlling lymphocyte growth and selection. We identified proteins that are involved in anti-IgM **antibody**-mediated apoptosis using a subclone of the human Burkitt lymphoma cell line BL60. Apoptosis-associated ...

... following 12 apoptosis-associated proteins were identified: heterogeneous nuclear ribonucleoprotein (hnRNP) A1, hnRNP C1/C2, **FUSE**-binding protein, dUTPase, lymphocyte-specific protein LSP1, UV excision repair protein RAD23 homologue B (HHR23B...

... Asp(OMe)-Glu(OMe)-Val-Asp(OMe)-fluoromethyl ketone, a selective irreversible inhibitor of CPP32 (**caspase 3**).

Descriptors: Apoptosis; *Burkitt Lymphoma--metabolism--ME; * **Caspases**--metabolism--ME; *Neoplasm Proteins--metabolism--ME; *Ribonucleoproteins--metabolism--ME; Calcium-Binding Proteins--metabolism --ME; **Caspases**--antagonists and inhibitors--AI; Chromosomal Proteins, Non-Histone--metabolism--ME; DNA-Binding Proteins--metabolism--ME...
Enzyme No.: EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**) ; EC 3.6.1.- (Pyrophosphatases); EC 3.6.1.23 (dUTP pyrophosphatase)
...Chemical Name: nucleolin; phosphoprotein P0; heterochromatin-specific nonhistone chromosomal protein HP-1; RAD23 protein, human; CPP32 protein; **Caspases**; Pyrophosphatases; dUTP pyrophosphatase

12/3,K,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11539384 98430705 PMID: 9759905
Therapeutic preparations of normal polyspecific IgG (IVIg) induce apoptosis in human lymphocytes and monocytes: a novel mechanism of action of IVIg involving the Fas apoptotic pathway.
Prasad N K; Papoff G; Zeuner A; Bonnin E; Kazatchkine M D; Ruberti G; Kaveri S V
Institut National de la Sante et de la Recherche Medicale U430, Universite Pierre et Marie Curie, Paris, France.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Oct 1 **1998**, 161 (7) p3781-90, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Therapeutic preparations of normal human IgG for i.v. use (i.v.Ig) exhibit a broad spectrum of immunoregulatory activities in vitro and in vivo. I.v.Ig has been shown to inhibit the proliferation of activated B and T lymphocytes and of several autonomously growing cell lines. In this study, we demonstrate that i.v.Ig induces apoptosis in leukemic cells of lymphocyte and monocyte lineage and in CD40-activated normal tonsillar B cells, involving, at least in part, Fas (CD95/APO-1) and activation of **caspases** . I.v.Ig-induced apoptosis was higher in Fas-sensitive HuT78 cells than in Fas-resistant HuT78.B1 mutant cells, and soluble Fas inhibited IVIg-induced apoptosis. I.v.Ig immunoprecipitated Fas from Fas-expressing transfectants and recognized purified Fas/glutathione-S-transferase **fusion** proteins upon immunoblotting. Affinity-purified anti-Fas Abs from i.v.Ig induced apoptosis of CEM T cells at a 120-fold lower concentration than unfractionated i.v.Ig. Inhibitors of cysteine proteases of the **caspase** family, **caspase** 1 (IL-1beta-converting enzyme) and **caspase 3** (Yama/CPP32b), partially inhibited i.v.Ig-induced apoptosis of CEM cells. Furthermore, cleavage of poly(A)DP-ribose polymerase into an 85-kDa signature death fragment was observed in CEM cells following i.v.Ig treatment. Thus, normal IgG induces apoptosis in lymphocytes and monocytes. Our results provide evidence for a role of Fas, bring new insights into the mechanisms of action of i.v.Ig in autoimmune diseases, and suggest a role of normal Ig in controlling cell death and proliferation.

Oct 1 **1998**,
... tonsillar B cells, involving, at least in part, Fas (CD95/APO-1) and activation of **caspases** . I.v.Ig-induced apoptosis was higher in Fas-sensitive HuT78 cells than in Fas...
... v.Ig immunoprecipitated Fas from Fas-expressing transfectants and recognized purified Fas/glutathione-S-transferase **fusion** proteins upon immunoblotting. Affinity-purified anti-Fas Abs from i.v.Ig induced apoptosis of...

... 120-fold lower concentration than unfractionated i.v.Ig. Inhibitors of

cysteine proteases of the **caspase** family, **caspase** 1 (IL-1beta-converting enzyme) and **caspase 3** (Yama/CPP32b), partially inhibited i.v.Ig-induced apoptosis of CEM cells. Furthermore, cleavage of...
Descriptors: **Antibody** Specificity; *Antigens, CD95--physiology--PH; *Apoptosis--immunology--IM; *B-Lymphocytes--cytology--CY; *Immunoglobulins, Intravenous--pharmacology...

12/3,K,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11439475 98322475 PMID: 9658339
Thrombin is an extracellular signal that activates intracellular death protease pathways inducing apoptosis in model motor neurons.
Smirnova I V; Zhang S X; Citron B A; Arnold P M; Festoff B W
Neurobiology Research Laboratory (151R), Department of Veterans Affairs Medical Center, Kansas City, Missouri 64128, USA.
Journal of neurobiology (UNITED STATES) Jul **1998**, 36 (1) p64-80, ISSN 0022-3034 Journal Code: 0213640
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Apoptosis, often also termed "programmed cell death", occurs in normal development in the brain and spinal cord. Important to concepts of disease and potential intervention is the exciting finding that apoptosis is also found after neurotrauma and in a number of neurodegenerative diseases. Although the precise mechanism of neuronal cell loss remains unknown, much emphasis has been placed recently on the activation of cell death protease cascades within the cell. How these cascades may be activated, especially from extracellular influences, is currently poorly understood. Thrombin, the multifunctional coagulation protease, is an early phase modulator at sites of tissue injury and has been shown to induce cell death in neurons by an apoptotic mechanism by activating its receptor, PAR-1. Using a model motor neuronal cell line, NSC19, which we have shown undergoes apoptosis after treatment with classic apoptosis inducers such as the topoisomerase inhibitors camptothecin and etoposide, we unambiguously found that nanomolar thrombin induced characteristic signs of apoptosis. Strikingly, endonucleolysis was accompanied by an increase in **caspase**-3 -like activity in cellular extracts, which correlated with both detection of **caspase** -induced signature cleavage of the cortical cytoskeleton component nonerythroid spectrin (alpha-fodrin) and identification of increased accessibility of a **caspase** cleavage domain, using an **antibody** (Ab127) made against a synthetic peptide KGDEVD. Demonstrating that thrombin activation of death proteases was **linked** to cell death, we were able to inhibit thrombin-induced apoptosis by using a **caspase** family inhibitor, benzyloxycarbonyl-Asp-(oMe)-fluoromethyl ketone (Boc-D-FMK). These novel results demonstrate that thrombin serves as an extracellular "death signal" to activate intracellular protease pathways. These pathways lead to apoptotic cell death and can be modulated by inhibiting **caspase** activity downstream to PAR-1.

Jul **1998**,
... nanomolar thrombin induced characteristic signs of apoptosis. Strikingly, endonucleolysis was accompanied by an increase in **caspase** -3 -like activity in cellular extracts, which correlated with both detection of **caspase** -induced signature cleavage of the cortical cytoskeleton component nonerythroid spectrin (alpha-fodrin) and identification of increased accessibility of a **caspase** cleavage domain, using an **antibody** (Ab127) made against a synthetic peptide KGDEVD. Demonstrating that thrombin activation of death proteases was **linked** to cell death, we were able to inhibit thrombin-induced

apoptosis by using a **caspase** family inhibitor, benzyloxycarbonyl-Asp-(oMe)-fluoromethyl ketone (Boc-D-FMK). These novel results demonstrate that...

... protease pathways. These pathways lead to apoptotic cell death and can be modulated by inhibiting **caspase** activity downstream to PAR-1.

12/3,K,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11369881 98250765 PMID: 9582351
Regulation of protein phosphatase 2A activity by **caspase-3** during apoptosis.
Santoro M F; Annand R R; Robertson M M; Peng Y W; Brady M J; Mankovich J A; Hackett M C; Ghayur T; Walter G; Wong W W; Giegel D A
Department of Biochemistry, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105, USA.
Journal of biological chemistry (UNITED STATES) May 22 **1998**, 273 (21) p13119-28, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Although the available evidence suggests that whereas the **caspase** family plays a major role in apoptosis, they are not the sole stimulators of death. A random yeast two-hybrid screen of a lymphocyte cDNA library (using **caspase-3** as the bait) found an interaction between **caspase-3** and the regulatory subunit Aalpha of protein phosphatase 2A. This protein was found to be a substrate for **caspase-3**, but not **caspase** -1, and could compete effectively against either a protein or synthetic peptide substrate. In Jurkat cells induced to undergo apoptosis with anti-Fas **antibody** , protein phosphatase 2A (PP2A) activity increased 4.5-fold after 6 h. By 12 h, the regulatory Aalpha subunit could no longer be detected in cell lysates. There was no change in the amount of the catalytic subunit. The effects on PP2A could be prevented by the **caspase** family inhibitors acetyl-Asp-Glu-Val-Asp (DEVD) aldehyde or Ac-DEVD fluoromethyl ketone. The mitogen-activated protein (MAP) kinase pathway is regulated by PP2A. At 12 h after the addition of anti-Fas **antibody** , a decrease in the amount of the phosphorylated forms of MAP kinase was observed. Again, this loss of activated MAP kinase could be prevented by the addition of DEVD-cho or DEVD-fmk. These data are consistent with a pathway whereby induction of apoptosis activates **caspase-3** . This enzyme then cleaves the regulatory Aalpha subunit of PP2A, increasing its activity. These data show that the activated PP2A will then effect a change in the phosphorylation state of the cell. These data provide a **link** between the **caspases** and signal transduction pathways.

Regulation of protein phosphatase 2A activity by **caspase-3** during apoptosis.
May 22 **1998**,
Although the available evidence suggests that whereas the **caspase** family plays a major role in apoptosis, they are not the sole stimulators of death. A random yeast two-hybrid screen of a lymphocyte cDNA library (using **caspase-3** as the bait) found an interaction between **caspase-3** and the regulatory subunit Aalpha of protein phosphatase 2A. This protein was found to be a substrate for **caspase-3**, but not **caspase** -1, and could compete effectively against either a protein or synthetic peptide substrate. In Jurkat cells induced to undergo apoptosis with anti-Fas **antibody** , protein phosphatase 2A (PP2A) activity increased 4.5-fold after 6 h. By 12 h...

... the amount of the catalytic subunit. The effects on PP2A could be prevented by the **caspase** family inhibitors acetyl-Asp-Glu-Val-Asp (DEVD) aldehyde or Ac-DEVD fluoromethyl ketone. The...

... kinase pathway is regulated by PP2A. At 12 h after the addition of anti-Fas **antibody** , a decrease in the amount of the phosphorylated forms of MAP kinase was observed. Again...

... or DEVD-fmk. These data are consistent with a pathway whereby induction of apoptosis activates **caspase-3**. This enzyme then cleaves the regulatory Aalpha subunit of PP2A, increasing its activity. These data...

... then effect a change in the phosphorylation state of the cell. These data provide a **link** between the **caspases** and signal transduction pathways.

12/3,K,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11265387 98143751 PMID: 9485209
Inhibition of CPP32 blocks surface IgM-mediated apoptosis and D4-GDI cleavage in human BL60 Burkitt lymphoma cells.
Rickers A; Brockstedt E; Mapara M Y; Otto A; Dorken B; Bommert K
Max Delbruck Center for Molecular Medicine, Berlin-Buch, Germany.
European journal of immunology (GERMANY) Jan **1998**, 28 (1) p296-304, ISSN 0014-2980 Journal Code: 1273201
Erratum in Eur J Immunol 1998 Mar;28(3) 1122
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Apoptosis (programmed cell death) is instrumental in the process of controlling lymphocyte growth and selection. Negative selection, mediated by surface IgM (sIgM) signaling after encountering self antigen, eliminates autoreactive B cells. To identify proteins which are potentially involved in anti-IgM-mediated apoptosis, we used an anti-IgM-sensitive subclone of the human Burkitt lymphoma cell line BL60. After anti-IgM treatment and separation of apoptosis-committed cells, we performed high resolution two-dimensional gel electrophoresis (2-DE). Comparison of the 2-DE protein patterns from apoptotic and non-apoptotic cells showed differences in approximately 80 spots. Subsequent analysis of these proteins was performed by mass spectrometry and Edman microsequencing. We report that one of these spots which disappears after sIgM cross-**linking** turned out to be D4-GDI. D4-GDI is an abundant hematopoietic cell GDP dissociation inhibitor for the Ras-related Rho family GTPase. D4-GDI was rapidly truncated to a 23-kDa fragment in BL60 cells. By using a Rho-GDI-specific antiserum, which cross-reacts with D4-GDI, we observed the onset of cleavage after 8 h of stimulation with anti-IgM. Cleavage and apoptosis could be completely inhibited by z-DEVD-fmk, a selective irreversible inhibitor of CPP32 (**caspase-3**), whereas ac-YVAD-cmk, an inhibitor for interleukin-1beta-converting enzyme-like proteases, did not block cleavage of D4-GDI or apoptosis. Our results revealed the functional importance of **caspases** and a new target protein in the process of anti-IgM-mediated apoptosis.

Jan **1998**,
... and Edman microsequencing. We report that one of these spots which disappears after sIgM cross-**linking** turned out to be D4-GDI. D4-GDI is an abundant hematopoietic cell GDP dissociation...

... apoptosis could be completely inhibited by z-DEVD-fmk, a selective irreversible inhibitor of CPP32 (**caspase-3**), whereas

ac-YVAD-cmk, an inhibitor for interleukin-1beta-converting enzyme-like proteases, did not block cleavage of D4-GDI or apoptosis. Our results revealed the functional importance of **caspases** and a new target protein in the process of anti-IgM-mediated apoptosis.

; Amino Acid Chloromethyl Ketones--pharmacology--PD; **Antibodies**, Anti-Idiotypic--pharmacology--PD; Cysteine Proteinase Inhibitors --pharmacology--PD; Electrophoresis, Gel, Two-Dimensional; Immunomagnetic Separation...

Chemical Name: Amino Acid Chloromethyl Ketones; **Antibodies** , Anti-Idiotypic; Cysteine Proteinase Inhibitors; Immunoglobulin M; Immunoglobulins, Surface; N-acetyl-tyrosyl-valyl-alanyl-aspartyl...

12/3,K,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11245569 98123110 PMID: 9452459

Bcl-xL acts downstream of **caspase** -8 activation by the CD95 death-inducing signaling complex.

Medema J P; Scaffidi C; Krammer P H; Peter M E

Tumor Immunology Program, German Cancer Research Center, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany.

Journal of biological chemistry (UNITED STATES) Feb 6 **1998**, 273 (6) p3388-93, ISSN 0021-9258 Journal Code: 2985121R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The Bcl-2 family member Bcl-xL has often been correlated with apoptosis resistance. We have shown recently that in peripheral human T cells resistance to CD95-mediated apoptosis is characterized by a lack of **caspase** -8 recruitment to the CD95 death-inducing signaling complex (DISC) and by increased expression of Bcl-xL (Peter, M. E., Kischkel, F. C., Scheuerpflug, C. G., Medema, J. P., Debatin, K.-M., and Krammer, P. H. (1997) Eur. J. Immunol. 27, 1207-1212). This raises the possibility that Bcl-xL directly prevents **caspase**-8 activation by the DISC. To test this hypothesis a cell line in which CD95 signaling was inhibited by overexpression of Bcl-xL was used. In these MCF7-Fas-bcl-xL cells Bcl-xL had no effect on the recruitment of **caspase**-8 to the DISC. It did not affect the activity of the DISC nor the generation of the **caspase**-8 active subunits p18 and p10. In contrast, cleavage of a typical substrate for **caspase**-3-like proteases, poly(ADP-ribose) polymerase, was inhibited in comparison with the control-transfected CD95-sensitive MCF7-Fas cells. To test whether Bcl-xL would inhibit active **caspase**-8 subunits in the cytoplasm, a number of immunoprecipitation experiments were performed. Using monoclonal **antibodies** directed against different domains of **caspase**-8, anti-Bcl-xL **antibodies**, or **fusion** proteins of glutathione S-transferase with different domains of **caspase** -8, no evidence for a direct or indirect physical interaction between **caspase** -8 and Bcl-xL was found. Moreover, overexpression of Bcl-xL did not inhibit the activity of the **caspase**-8 active subunits p18/p10. Therefore, in this cell line that has become resistant to CD95-induced apoptosis due to overexpression of Bcl-xL, Bcl-xL acts independently and downstream of **caspase**-8.

Bcl-xL acts downstream of **caspase** -8 activation by the CD95 death-inducing signaling complex.

Feb 6 **1998**,

... peripheral human T cells resistance to CD95-mediated apoptosis is characterized by a lack of **caspase** -8 recruitment to the CD95 death-inducing signaling complex (DISC) and by increased expression of...

...Eur. J. Immunol. 27, 1207-1212). This raises the possibility that Bcl-xL

directly prevents **caspase** -8 activation by the DISC. To test this hypothesis a cell line in which CD95...

...these MCF7-Fas-bcl-xL cells Bcl-xL had no effect on the recruitment of **caspase**-8 to the DISC. It did not affect the activity of the DISC nor the generation of the **caspase** -8 active subunits p18 and p10. In contrast, cleavage of a typical substrate for **caspase-3**-like proteases, poly(ADP-ribose) polymerase, was inhibited in comparison with the control-transfected CD95-sensitive MCF7-Fas cells. To test whether Bcl-xL would inhibit active **caspase**-8 subunits in the cytoplasm, a number of immunoprecipitation experiments were performed. Using monoclonal **antibodies** directed against different domains of **caspase**-8, anti-Bcl-xL **antibodies**, or **fusion** proteins of glutathione S-transferase with different domains of **caspase**-8, no evidence for a direct or indirect physical interaction between **caspase**-8 and Bcl-xL was found. Moreover, overexpression of Bcl-xL did not inhibit the activity of the **caspase** -8 active subunits p18/p10. Therefore, in this cell line that has become resistant to...
... induced apoptosis due to overexpression of Bcl-xL, Bcl-xL acts independently and downstream of **caspase**-8.
...Enzyme No.: 30 (Poly(ADP-ribose) Polymerases); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.22.- (**caspase** 8)
...Chemical Name: Proto-Oncogene Proteins c-bcl-2; bcl-x protein; Poly(ADP-ribose) Polymerases; Cysteine Endopeptidases; **caspase** 8

12/3,K,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08747619 20027820 PMID: 10556977
Tissue transglutaminase is a **caspase** substrate during apoptosis. Cleavage causes loss of transamidating function and is a biochemical marker of **caspase 3** activation.
Fabbi M; Marimpietri D; Martini S; Brancolini C; Amoresano A; Scaloni A; Bargellesi A; Cosulich E
Istituto Nazionale per la Ricerca sul Cancro, L.go R.Benzi 10, 16132 Genova, Italy. fabbi@ermes.cba.unige.it
Cell death and differentiation (ENGLAND) Oct **1999**, 6 (10) p992-1001, ISSN 1350-9047 Journal Code: 9437445
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Tissue transglutaminase (tTG) is a Ca2+-dependent cross-**linking** enzyme that participates in the apoptotic machinery by irreversibly assembling a protein scaffold that prevents the leakage of intracellular components. In the present study a single-chain **antibody** fragment (scFv) detecting tTG is described. We demonstrate that TG/F8 scFv, selected from a phase display library of human V-gene segments by binding to guinea-pig liver tTG, can react with human tTG both in Western blot and in immunohistochemistry. The specific detection of tTG by TG/F8 in human thymocytes is verified by mass spectrometric analysis of the purified protein. Furthermore, we demonstrate that in lymphoid cells tTG is cleaved by **caspase 3** during the late phase of apoptotic death, concomitant to DNA fragmentation, and that such cleavage causes loss of cross-**linking** function. We propose tTG cleavage as a valuable biochemical marker of **caspase 3** activation during the late execution phase of apoptosis.

Tissue transglutaminase is a **caspase** substrate during apoptosis. Cleavage causes loss of transamidating function and is a biochemical marker of **caspase 3** activation.
Oct **1999**,

Tissue transglutaminase (tTG) is a Ca2+-dependent cross-**linking** enzyme that participates in the apoptotic machinery by irreversibly assembling a protein scaffold that prevents the leakage of intracellular components. In the present study a single-chain **antibody** fragment (scFv) detecting tTG is described. We demonstrate that TG/F8 scFv, selected from a...

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Descriptors: Apoptosis--physiology--PH; ***Caspases**--metabolism--ME; *GTP-Binding Proteins--metabolism--ME; *Transglutaminases--metabolism--ME

...Enzyme No.: 2.3.2.13 (Transglutaminases); EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**); EC 3.6.1.- (GTP-Binding Proteins)

Chemical Name: Biological Markers; transglutaminase 2; Transglutaminases; CPP32 protein; **Caspases**; GTP-Binding Proteins

12/3,K,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08726432 20005705 PMID: 10537313

Characterization of glycosylphosphatidylinositol-**linked** molecule CD55/decay-accelerating factor as the receptor for **antibody** SC-1-induced apoptosis.

Hensel F; Hermann R; Schubert C; Abe N; Schmidt K; Franke A; Shevchenko A ; Mann M; Muller-Hermelink H K; Vollmers H P

Institut fur Pathologie, Wurzburg, Germany.

Cancer research (UNITED STATES) Oct 15 **1999**, 59 (20) p5299-306 , ISSN 0008-5472 Journal Code: 2984705R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The human monoclonal **antibody** SC-1 induces apoptosis of stomach carcinoma cells and is currently used in a clinical Phase II trial. The **antibody** binds to a target molecule that is preferentially expressed on diffuse- and intestinal-type stomach cancer cells and shows a very restricted expression on other normal and malignant tissues. In this paper, we show that the SC-1 receptor is a stomach carcinoma-associated isoform of CD55 [membrane-bound decay-accelerating factor (DAF)-B] with a relative molecular mass of approximately 82 kDa. The antigenic site of SC-1 is an N-**linked** carbohydrate residue. Cross-**linking** of the DAF receptor increases apoptotic activity. SC-1 binding induces tyrosine phosphorylation of three proteins of approximately 60, 75, and 110 kDa, whereas a serine residue of an approximately 35-kDa protein is dephosphorylated. Expression of **caspase-3** (CPP32) and **caspase**-8 (FLICE) is elevated, and activation of these **caspases** occurs. These data show that a tumor-specific variant form DAF is involved in apoptosis and can be used for adjuvant therapeutical purposes on gastric carcinoma.

Characterization of glycosylphosphatidylinositol-**linked** molecule CD55/decay-accelerating factor as the receptor for **antibody** SC-1-induced apoptosis.

Oct 15 **1999**,

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Descriptors: **Antibodies**, Monoclonal--metabolism--ME; * **Antibodies**, Neoplasm--metabolism--ME; *Antigens, CD55--physiology--PH ; *Apoptosis; *Glycosylphosphatidylinositols--physiology--PH; *Stomach Neoplasms--immunology--IM; **Antibodies**, Neoplasm --isolation and purification--IP; Antigens, CD55--isolation and purification--IP; **Caspases**--metabolism--ME; Glycoside Hydrolases--pharmacology--PD; Phospholipase C--pharmacology--PD; Phosphorylation; Stomach Neoplasms --pathology--PA...
...Enzyme No.: 1.4.3 (Phospholipase C); EC 3.2.1. (Glycoside Hydrolases); EC 3.4.22.- (**Caspases**)
Chemical Name: **Antibodies**, Monoclonal; **Antibodies**, Neoplasm; Antigens, CD55; Glycosylphosphatidylinositols; 1-phosphatidylinositol phosphodiesterase; Phospholipase C; Glycoside Hydrolases; **Caspases**

12/3,K,AB/20 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

11351115 BIOSIS NO.: 199800132447
Bcl-x|L acts downstream of **caspase**-8 activation by the CD95 death-inducing signaling complex.
AUTHOR: Medema Jan Paul; Scaffidi Carsten; Krammer Peter H; Peter Marcus E (a)
AUTHOR ADDRESS: (a)Tumor Immunol. Program, German Cancer Res. Cent., Im Neuenheimer Feld 280, 69120 Heidelberg**Germany
JOURNAL: Journal of Biological Chemistry 273 (6):p3388-3393 Feb. 6, **1998**
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The Bcl-2 family member Bcl-x|L has often been correlated with apoptosis resistance. We have shown recently that in peripheral human T cells resistance to CD95-mediated apoptosis is characterized by a lack of **caspase**-8 recruitment to the CD95 death-inducing signaling complex (DISC) and by increased expression of Bcl-x|L (Peter, M. E., Kischkel, F. C., Scheuerpflug, C. G., Medema, J. P., Debatin, K.-M., and Krammer, P. H. (1997) Eur. J. Immunol. 27,1207-1212). This raises the possibility that Bcl-x|L directly prevents **caspase**-8 activation by the DISC. To test this hypothesis a cell line in which CD95 signaling was inhibited by overexpression of Bcl-x|L was used. In these MCF7-Fas-bcl-x|L cells Bcl-x|L had no effect on the recruitment of **caspase**-8 to the DISC. It did not affect the activity of the DISC nor the generation of the **caspase**-8 active subunits p18 and p10. In contrast, cleavage of a typical substrate for **caspase-3**-like proteases, poly(ADP-ribose) polymerase, was inhibited in comparison with the control-transfected CD95-sensitive MCF7-Fas cells. To test whether Bcl-x|L would inhibit active **caspase**-8 subunits in the cytoplasm, a number of immunoprecipitation experiments were performed. Using monoclonal **antibodies** directed against different domains of **caspase**-8, anti-Bcl-x|L **antibodies**, or **fusion** proteins of glutathione S-transferase with different domains of **caspase**-8,

no evidence for a direct or indirect physical interaction between **caspase**-8 and Bcl-x|L was found. Moreover, overexpression of Bcl-x|L did not inhibit the activity of the **caspase**-8 active subunits p18/p10. Therefore, in this cell line that has become resistant to CD95-induced-apoptosis due to overexpression of Bcl-x|L, Bcl-x|L acts independently, and downstream of **caspase**-8.

1998
Bcl-x|L acts downstream of **caspase**-8 activation by the CD95 death-inducing signaling complex.
1998

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...due to overexpression of Bcl-x|L, Bcl-x|L acts independently, and downstream of **caspase**-8.
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **caspase**-8...

12/3,K,AB/21 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08159714 Genuine Article#: 252ZL Number of References: 40
Title: Selective loss of poly(ADP-ribose) and the 85-kDa fragment of poly(ADP-ribose) polymerase in nucleoli during alkylation-induced apoptosis of HeLa cells (ABSTRACT AVAILABLE)
Author(s): AlvarezGonzalez R (REPRINT) ; Spring H; Muller M; Burkle A
Corporate Source: UNIV N TEXAS,HLTH SCI CTR, DEPT MOL BIOL & IMMUNOL/FT WORTH//TX/76107 (REPRINT); UNIV N TEXAS,HLTH SCI CTR, INST CANC RES/FT WORTH//TX/76107; GERMAN CANC RES CTR,DIV TUMOR VIROL/D-6900 HEIDELBERG//GERMANY/; GERMAN CANC RES CTR,BIOMED STRUCT ANAL UNIT/D-6900 HEIDELBERG//GERMANY/
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, **1999**, V274, N45 (NOV 5), P 32122-32126
ISSN: 0021-9258 Publication date: 19991105
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Abstract: Alkylation treatment of HeLa cells results in the rapid induction

of apoptosis as revealed by DNA laddering and cleavage of poly(ADP-ribose) polymerase (PARP) into the 29-and 85-kDa fragments (Kumari S. R., Mendoza-Alvarez, H. & Alvarez-Gonzalez, R, (1998) Cancer Res. 58, 5075-5078). Here, we performed a time-course analysis of (i) poly(ADP-ribose) synthesis and degradation as well as (ii) the subnuclear localization of PARP and its fragments by using confocal laser scanning immunofluorescence microscopy, PARP was activated within 15 min post-treatment, as revealed by nuclear immunostaining with **antibody** 10H (recognizing poly(ADP-ribose)), This was followed by a late, time-dependent, progressive decline of 10H signals that coincide with the time of PARP cleavage. Strikingly, nucleolar immunostaining with **antibodies** 10H and C-LI-IO (recognizing the 85-kDa PARP fragment) was lost by 15 min post-treatment, whereas F-I-23 signals (recognizing the 29-kDa fragment) persisted. We hypothesize that the 85-kDa PARP fragment is translocated, along with covalently bound poly(ADP-ribose), from nucleoli to the nucleoplasm, whereas the 29-kDa fragment is retained, because it binds to DNA strand breaks. Our data (i) provide a **Link** between the known time-dependent bifunctional role of PARP in apoptosis and the subcellular localization of PARP fragments and also (ii) add to the evidence for early proteolytic changes in nucleoli during apoptosis.

, **1999**
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...Identifiers--DNA-BINDING; ADP-RIBOSE; CLEAVAGE; DAMAGE; IDENTIFICATION; **CASPASE-3**; INHIBITOR; SUBSTRATE; KINETICS; DOMAINS

12/3,K,AB/22 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07820405 Genuine Article#: 212CF Number of References: 78
Title: **Caspase**-mediated proteolysis and activation of protein kinase C delta plays a central role in neutrophil apoptosis (ABSTRACT AVAILABLE)
Author(s): Khwaja A (REPRINT) ; Tatton L
Corporate Source: UNIV COLL LONDON,SCH MED, DEPT HAEMATOL, 98 CHENIES MEWS/LONDON WC1E 6HX//ENGLAND/ (REPRINT)
Journal: BLOOD, **1999**, V94, N1 (JUL 1), P291-301
ISSN: 0006-4971 Publication date: 19990701
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399
Language: English Document Type: ARTICLE
Abstract: Neutrophils undergo constitutive apoptosis when aged ex vivo, Recent studies have indicated roles for Fas/CD95 and the nicotinamide adenine dinucleotide phosphate (NADPH)oxidase system in this process. We have investigated the role of protein kinase C (PKC) in neutrophil death. We show that there is proteolysis and activation of the novel isoform PKC delta in aged neutrophils and that this process is accelerated by the addition of an agonistic Fas **antibody**. PKC delta proteolysis occurs before the onset of any detectable features of apoptosis and pharmacologic inhibition of this enzyme inhibits neutrophil apoptosis. PKC delta cleavage and activation is dependent on

caspase-8/FADD-like interleukin-1 beta converting enzyme (FLICE)-mediated processing of **caspase**-3/CPP32. Neutrophil survival is prolonged by the addition of broad spectrum (BD.fmk) or **caspase**-8 targeted (zIETD.fmk) peptide **caspase** inhibitors. Inhibition of PKC delta does not prevent apoptosis triggered by factor withdrawal in immature hematopoietic cells, including normal human CD34(+) progenitors indicating that within a given lineage, the mechanisms of apoptosis may be differentiation-stage-specific. Ex vivo aging of neutrophils leads to the increasing production of reactive oxygen species and this is attenuated in cells treated with either **caspase** or PKC delta inhibitors. Proteolytically activated PKC delta acts as a molecular **link** between the Fas/CD95 receptor and the NADPH-oxidase system and plays a central role in regulating the process of neutrophil apoptosis. (C) 1999 by The American Society of Hematology.

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...Abstract: aged neutrophils and that this process is accelerated by the addition of an agonistic Fas **antibody**. PKC delta proteolysis occurs before the onset of any detectable features of apoptosis and pharmacologic inhibition of this enzyme inhibits neutrophil apoptosis. PKC delta cleavage and activation is dependent on **caspase**-8/FADD-like interleukin-1 beta converting enzyme (FLICE)-mediated processing of **caspase**-3/CPP32. Neutrophil survival is prolonged by the addition of broad spectrum (BD.fmk) or **caspase**-8 targeted (zIETD.fmk) peptide **caspase** inhibitors. Inhibition of PKC delta does not prevent apoptosis triggered by factor withdrawal in immature...

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12/3,K,AB/23 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07490243 Genuine Article#: 172YY Number of References: 39
Title: Establishment of a mutant from human monocytic leukaemia U937 that exhibits a genetically dominant resistance to TNF alpha-induced apoptosis (ABSTRACT AVAILABLE)
Author(s): Dong J; Naito M; Dan S; Tsuruo T (REPRINT)
Corporate Source: UNIV TOKYO,INST MOL & CELLULAR BIOSCI, BUNKYO KU, YAYOI 1-1-1/TOKYO 113//JAPAN/ (REPRINT); UNIV TOKYO,INST MOL & CELLULAR BIOSCI, BUNKYO KU/TOKYO 113//JAPAN/; JAPANESE FDN CANC RES,CTR CANC CHEMOTHERAPY, TOSHIMA KU/TOKYO 170//JAPAN/
Journal: APOPTOSIS, **1998**, V3, N4 (SEP), P245-254
ISSN: 1360-8185 Publication date: 19980900
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: Tumour necrosis factor-alpha (TNF alpha) is a cytokine that induces apoptosis in various cell systems by binding to a TNF receptor (TNFR). To study TNF alpha-induced apoptosis, we isolated and characterized a novel TNF alpha resistant variant, U937/TNF clone IL-5, from human monocytic leukaemia U937 cells. The IL-5 cells resist apoptosis by TNF alpha and anti-Fas **antibody** but not by anticancer drugs, such as VP-16 and Ara-C. Somatic cell hybridization between U937 and IL-5 showed that the apoptosis resistance to TNF alpha

in IL-5 was genetically dominant. This dominant mutation in IL-5 cells blocks TNF alpha-induced disruption of mitochondrial membrane potential and **caspase-3** activation. Expression of TNPR, Fas and Bcl-2 family proteins were not changed in IL-5 cells. These results suggest that the apoptosis-resistant IL-5 cells could have a functional defect in apoptosis signalling from TNFR to mitochondria and **caspase** activation. The IL-5 cells could be useful in studying the signalling **linkage** between TNPR and mitochondria.

, **1998**

...Abstract: leukaemia U937 cells. The IL-5 cells resist apoptosis by TNF alpha and anti-Fas **antibody** but not by anticancer drugs, such as VP-16 and Ara-C. Somatic cell hybridization...

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12/3,K,AB/24 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07416587 Genuine Article#: 163EU Number of References: 54
Title: Chemotherapy augments TRAIL-induced apoptosis in breast cell lines (ABSTRACT AVAILABLE)
Author(s): Keane MM; Ettenberg SA; Nau MM; Russell EK; Lipkowitz S (REPRINT)
Corporate Source: NCI,DIV CLIN SCI, MED BRANCH, NATL NAVAL MED CTR, BLDG 8, ROOM 5101/BETHESDA//MD/20889 (REPRINT); NCI,DIV CLIN SCI, MED BRANCH, NATL NAVAL MED CTR/BETHESDA//MD/20889
Journal: CANCER RESEARCH, **1999**, V59, N3 (FEB 1), P734-741
ISSN: 0008-5472 Publication date: 19990201
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE
Abstract: Expression and function of the TRAIL apoptotic pathway was investigated in normal and malignant breast epithelial cells. Glutathione-S-transferase (GST)-TRAIL extracellular domain **fusion** proteins Here produced to analyze TRAIL-induced apoptosis. Only GST-TRAIL constructs containing regions homologous to the Fas self-association and ligand binding domains could induce apoptosis, GST-TRAIL induced significant (>90%) apoptosis in just one of eight normal and one of eight malignant breast cell lines. All other lines were relatively resistant to TRAIL-induced apoptosis, Activating TRAIL receptors DR I and DR5 were expressed in all normal and malignant breast cell lines. The inhibitory receptor TRID was highly expressed in one of tour normal and two of seven malignant breast cell lines, DR4, DR5, or TRID expression did not correlate with sensitivity to TRAIL-induced apoptosis. Incubation of cell lines with doxorubicin or 5-fluorouracil significantly augmented TRAIL-induced apoptosis in most breast cell lines, By fractional inhibition analysis, the toxicity of the combination of TRAIL and doxorubicin or 5-fluorouracil was synergistic compared with either agent alone. In contrast, melphalan and paclitaxel augmented TRAIL-induced apoptosis in few cell lines, and methotrexate did not augment it in any cell line. Augmentation of TRAIL-induced apoptosis by doxorubicin or 5-fluorouracil was mediated through **caspase** activation, This was evidenced by the fact that chemotherapy agents that synergized with TRAIL (e.g., doxorubicin)

themselves caused cleavage of **caspase**-3 and poly(ADP-ribose) polymerase (PARP), and their toxicity was blocked by the **caspase** inhibitor Z-Val-Ala-Asp(OMe)-CH2 (ZVAD-fmk), The combination of TRAIL and doxorubicin caused significantly greater **caspase**-3 and PARP cleavage, and the combined toxicity also was inhibited by ZVAD-fmk. In contrast, chemotherapy agents that did not augment TRAIL-induced apoptosis (e.g., methotrexate) caused minimal **caspase**-3 and PARP cleavage by themselves, and their toxicity was not inhibited by ZVAD-fmk, These drugs also did not increase **caspase**-3 or PARP cleavage when combined with TRAIL. Tn summary, few breast cell lines are sensitive to TRAIL-induced apoptosis, and no difference in sensitivity is found between normal and malignant cell lines. Treatment with chemotherapy provides an approach to sensitize breast cancer cells to TRAIL-induced apoptosis.

, **1999**
...Abstract: investigated in normal and malignant breast epithelial cells. Glutathione-S-transferase (GST)-TRAIL extracellular domain **fusion** proteins Here produced to analyze TRAIL-induced apoptosis. Only GST-TRAIL constructs containing regions homologous...

...cell line. Augmentation of TRAIL-induced apoptosis by doxorubicin or 5-fluorouracil was mediated through **caspase** activation, This was evidenced by the fact that chemotherapy agents that synergized with TRAIL (e.g., doxorubicin) themselves caused cleavage of **caspase**-3 and poly(ADP-ribose) polymerase (PARP), and their toxicity was blocked by the **caspase** inhibitor Z-Val-Ala-Asp(OMe)-CH2 (ZVAD-fmk), The combination of TRAIL and doxorubicin caused significantly greater **caspase**-3 and PARP cleavage, and the combined toxicity also was inhibited by ZVAD-fmk. In contrast, chemotherapy agents that did not augment TRAIL-induced apoptosis (e.g., methotrexate) caused minimal **caspase**-3 and PARP cleavage by themselves, and their toxicity was not inhibited by ZVAD-fmk, These drugs also did not increase **caspase**-3 or PARP cleavage when combined with TRAIL. Tn summary, few breast cell lines are sensitive...
...Identifiers--DRUG-INDUCED APOPTOSIS; ANTI-FAS **ANTIBODY**; APO-1/FAS RECEPTOR/LIGAND SYSTEM; WILD-TYPE P53; CANCER-CELLS; MEDIATED CYTOTOXICITY; MUTANT P53...

12/3,K,AB/25 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07336334 Genuine Article#: 152EV Number of References: 48
Title: Lipopolysaccharide stimulates butyric acid-induced apoptosis in human peripheral blood mononuclear cells (ABSTRACT AVAILABLE)
Author(s): KuritaOchiai T (REPRINT) ; Fukushima K; Ochiai K
Corporate Source: NIHON UNIV,SCH DENT, DEPT MICROBIOL/MATSUDO/CHIBA 2718587/JAPAN/ (REPRINT)
Journal: INFECTION AND IMMUNITY, **1999**, V67, N1 (JAN), P22-29
ISSN: 0019-9567 Publication date: 19990100
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171
Language: English Document Type: ARTICLE
Abstract: We previously reported that butyric acid, an extracellular metabolite from periodontopathic bacteria, induced apoptosis in murine thymocytes, splenic T cells, and human Jurkat T cells, In this study, we examined the ability of butyric acid to induce apoptosis in peripheral blood mononuclear cells (PBMC) and the effect of bacterial lipopolysaccharide (LPS) on this apoptosis. Butyric acid significantly inhibited the anti-CD3 monoclonal **antibody**- and concanavalin A-induced proliferative responses in a dose-dependent fashion. This inhibition of PBMC growth by butyric acid depended on apoptosis in

vitro. It was characterized by internucleosomal DNA digestion and revealed by gel electrophoresis followed by a colorimetric DNA fragmentation assay to occur in a concentration-dependent fashion. Butyric acid-induced PBMC apoptosis was accompanied by **caspase**-3 protease activity but not by **caspase**-1 protease activity. LPS potentiated butyric acid-induced PBMC apoptosis in a dose-dependent manner. Flow-cytometric analysis revealed that LPS increased the proportion of sub-G, cells and the number of late-stage apoptotic cells induced by butyric acid. Annexin V binding experiments with fractionated subpopulations of PBMC in flow cytometory revealed that LPS accelerated the butyric acid-induced CD3+-T-cell. apoptosis followed by similar levels of both CD4(+)- and CD8(+)-T-cell apoptosis. The addition of LPS to PBMC cultures did not cause DNA fragmentation, suggesting that LPS was unable to induce PBMC apoptosis directly. These data suggest that LPS, in combination with butyric acid, potentiates CD3(+) PBMC T-cell apoptosis and plays a role in the apoptotic depletion of CD4(+) and CD8(+) cells.

, **1999**
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...Identifiers--FATTY-ACIDS; T-CELLS; IN-VIVO; BACTERIAL-ENDOTOXIN; CERAMIDE GENERATION; ICE/CED-3 PROTEASE; CROSS-**LINKING**; NITRIC-OXIDE; DEATH

12/3,K,AB/26 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07169172 Genuine Article#: 132BJ Number of References: 55
Title: Villous cytotrophoblast regulation of the syncytial apoptotic cascade in the human placenta (ABSTRACT AVAILABLE)
Author(s): Huppertz B (REPRINT) ; Frank HG; Kingdom JCP; Reister F; Kaufmann P
Corporate Source: RHEIN WESTFAL TH AACHEN,INST ANAT, WENDLINGWEG 2/D-52057 AACHEN//GERMANY/ (REPRINT); UNIV TORONTO,MT SINAI HOSP, DEPT OBSTET & GYNAECOL/TORONTO/ON/CANADA/; TECH UNIV,DEPT OBSTET & GYNECOL/D-52057 AACHEN//GERMANY/
Journal: HISTOCHEMISTRY AND CELL BIOLOGY, **1998**, V110, N5 (NOV), P 495-508
ISSN: 0301-5564 Publication date: 19981100
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Abstract: Villous trophoblast in the human placenta consists of a population of proliferating stem cells which differentiate and individually **fuse** into the syncytiotrophoblast. We studied the apoptotic cascade in this complex epithelial layer by immunohistochemical localization of Fas, Fast, Bcl-2, Mcl-1, pro-**caspase**-3 and **caspase**-3, T-cell-restricted intracellular antigen-related protein (TIAR), poly(ADP-ribose) polymerase (PARP), lamin B, topoisomerase II alpha, and transglutaminase II in cryostat and paraffin-fixed tissue sections from, normal human first-trimester and term placental villi. The relationship between the apoptotic cascade and syncytial **fusion** was studied by coincubation of intact villi with FITC-coupled annexin-V, to detect the phosphatidylserine flip, and propidium iodide, to detect plasma membrane permeability. The final events of the

apoptotic cascade were studied by the TUNEL reaction and ultrastructural appearance of the trophoblast. The phosphatidylserine flip was identified in some of the villous cytotrophoblastic cells, but the presence of both Bcl-2 and Mcl-1 proteins presumably prevented continuation of the apoptotic cascade. The syncytiotrophoblast demonstrated heterogeneous findings, suggesting variable progression along the apoptotic cascade. In some areas Bcl-2 and Mcl-1 predominated, with preservation of the nuclear proteins PARP, lamin B, and topoisomerase II alpha; in other areas, especially in and around syncytial sprouts, Bcl-2 and Mcl-1 were absent, accompanied by loss of nuclear proteins, presence of phosphatidylserine flip, and TUNEL positivity. These data suggest that the apoptotic cascade is initiated in the villous cytotrophoblast, which in turn promotes syncytial **fusion**. Donation of anti-apoptotic proteins into the syncytium, such as Bcl-2 and Mcl-1, focally inhibits further progression along this cascade. Completion of the apoptotic cascade takes place in and around syncytial sprouts, providing further evidence that these are the sites of trophoblast shedding into the maternal circulation.

, **1998**
...Abstract: the human placenta consists of a population of proliferating stem cells which differentiate and individually **fuse** into the syncytiotrophoblast. We studied the apoptotic cascade in this complex epithelial layer by immunohistochemical localization of Fas, Fast, Bcl-2, Mcl-1, pro-**caspase**-3 and **caspase**-3, T-cell-restricted intracellular antigen-related protein (TIAR), poly(ADP-ribose) polymerase (PARP), lamin B...

...human first-trimester and term placental villi. The relationship between the apoptotic cascade and syncytial **fusion** was studied by coincubation of intact villi with FITC-coupled annexin-V, to detect the ...

...that the apoptotic cascade is initiated in the villous cytotrophoblast, which in turn promotes syncytial **fusion**. Donation of anti-apoptotic proteins into the syncytium, such as Bcl-2 and Mcl-1...
...Identifiers--PROGRAMMED CELL-DEATH; FAS LIGAND; SEQUENTIAL ACTIVATION; MONOCLONAL-**ANTIBODY**; MEDIATED APOPTOSIS; BCL-2 EXPRESSION; IN-VITRO; ICE-LIKE; PHOSPHATIDYLSERINE; TROPHOBLAST

12/3,K,AB/27 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06617440 Genuine Article#: ZE957 Number of References: 38
Title: Synthetic activation of **caspases**: Artificial death switches (ABSTRACT AVAILABLE)
Author(s): MacCorkle RA; Freeman KW; Spencer DM (REPRINT)
Corporate Source: BAYLOR COLL MED,DEPT MICROBIOL & IMMUNOL, 1 BAYLOR PLAZA, M929/HOUSTON//TX/77030 (REPRINT); BAYLOR COLL MED,DEPT MICROBIOL & IMMUNOL/HOUSTON//TX/77030
Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **1998**, V95, N7 (MAR 31), P3655-3660
ISSN: 0027-8424 Publication date: 19980331
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418
Language: English Document Type: ARTICLE
Abstract: The development of safe vectors for gene therapy requires fail-safe mechanisms to terminate therapy or remove genetically altered cells. The ideal ''suicide switch'' would be nonimmunogenic and nontoxic when uninduced and able to trigger cell death independent of tissue type or cell cycle stage, By using chemically induced dimerization, we have developed powerful death switches based on the

cysteine proteases, **caspase**-1 ICE (interleukin-1 beta converting enzyme) and **caspase-3** YAMA, In both cases, aggregation of the target protein is achieved by a nontoxic lipid-permeable dimeric FK506 analog that binds to the attached FK506-binding proteins, FKBPs. We find that intracellular cross-**linking** of **caspase**-1 or **caspase-3** is sufficient to trigger rapid apoptosis in a Bcl-x(L)-independent manner, suggesting that these conditional proapoptotic molecules can bypass intracellular checkpoint genes, such as Bcl-x(L), that limit apoptosis. Because these **chimeric** molecules are derived from autologous proteins, they should be nonimmunogenic and thus ideal for long-lived gene therapy vectors. These properties should also make chemically induced apoptosis useful for developmental studies, for treating hyperproliferative disorders, and for developing animal models to a wide variety of diseases.

Title: Synthetic activation of **caspases**: Artificial death switches , **1998**

...Abstract: using chemically induced dimerization, we have developed powerful death switches based on the cysteine proteases, **caspase** -1 ICE (interleukin-1 beta converting enzyme) and **caspase-3** YAMA, In both cases, aggregation of the target protein is achieved by a nontoxic lipid...

...analog that binds to the attached FK506-binding proteins, FKBPs. We find that intracellular cross-**linking** of **caspase**-1 or **caspase-3** is sufficient to trigger rapid apoptosis in a Bcl-x(L)-independent manner, suggesting that...

...can bypass intracellular checkpoint genes, such as Bcl-x(L), that limit apoptosis. Because these **chimeric** molecules are derived from autologous proteins, they should be nonimmunogenic and thus ideal for long...

...Identifiers--ANTI-FAS **ANTIBODY**; CELL-DEATH; SIGNAL-TRANSDUCTION; APOPTOSIS; RECEPTOR; PROTEASE; DIMERIZATION; THYMOCYTES; EXPRESSION; INTERACTS

?

Document Type: C
REGULATED APOPTOSIS; A GENETIC CONSTRUCT ENCODING A CHIMERIC PROTEIN HAVING AN ACTIVATABLE APOPTOSIS-DOMAIN TO COMPLEX WITH A NONPROTEIN, MEMBRANE-PERMEABLE **LIGAND** WHICH THEN BINDS TO ANOTHER PROTEIN THEREBY ACTIVATING THE APOPTOSIS-INDUCING DOMAIN
Inventors: Belshaw Peter (US); Crabtree Gerald R (US); Schreiber Stuart L (US); Spencer David M (US); Wandless Thomas J (US)
Assignee: Harvard College, President & Fellows of; Stanford, Leland Jr University Trustees
Assignee Code: 00542 49136 Document Type: REASSIGNED
Publication (No,Date), Applic (No,Date):
US 5834266 **19981110** US 94292597 19940818
Publication Kind: A
Calculated Expiration: 20151110
(Cited in 002 later patents)
Cont.-in-part Pub(No),Applic(No,Date): ABANDONED US 9317931 19930212; ABANDONED US 9392977 19930716; US 9393499 19930716; ABANDONED US 94179143 19940107; US 94179748 19940107
Priority Applic(No,Date): US 94292597 19940818; US 9317931 19930212; US 9392977 19930716; US 9393499 19930716; US 94179143 19940107; US 94179748 19940107

Abstract: We have developed a general procedure for the regulated (**inducible**) dimerization or **oligomerization** of intracellular proteins and disclose methods and materials for using that procedure to regulatably initiate cell-specific apoptosis (programmed cell death) in genetically engineered cells.

ialog Acc No: 3246316 IFI Acc No: 9942452
Document Type: C
REGULATED APOPTOSIS; USING A DNA
Inventors: Belshaw Peter (US); Crabtree Gerald R (US); Schreiber Stuart L (US); Spencer David M (US); Wandless Thomas J (US)
Assignee: Harvard College, President & Fellows of; Stanford, Leland Jr University Trustees
Assignee Code: 00542 49136
Publication (No,Date), Applic (No,Date):
US 5994313 **19991130** US 95483898 19950607
Publication Kind: A
Calculated Expiration: 20161130
(Cited in 002 later patents)
Cont.-in-part Pub(No),Applic(No,Date): ABANDONED US 9317931 19930212; ABANDONED US 9392977 19930716; ABANDONED US 9393499 19930716; ABANDONED US 94179748 19940107; ABANDONED US 94179143 19940117; ABANDONED US 94196043 19940214
Division Pub(No),Applic(No,Date): US 5834266 US 94292597 19940818
Priority Applic(No,Date): US 95483898 19950607; US 9317931 19930212; US 9392977 19930716; US 9393499 19930716; US 94179748 19940107; US 94179143 19940117; US 94196043 19940214; US 94292597 19940818

Abstract: We have developed a general procedure for the regulated (**inducible**) dimerization or **oligomerization** of intracellular proteins and disclose methods and materials for using that procedure to regulatably initiate cell-specific apoptosis (programmed cell death) in genetically engineered cells.

...15. The method of claim 1, wherein the chimeric protein comprises at least one **ligand**-binding domain comprising an immunophilin domain, cyclophilin domain, steroid binding domain, antibiotic binding domain, or an **antibody** domain16. The method of claim 1, wherein said at least one **ligand** binding domain is provided in the chimeric protein as an intracellular domain

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? s antibod? or ligand
         1349719  ANTIBOD?
          315946  LIGAND
      S1 1625787  ANTIBOD? OR LIGAND
? s oligomeri? (5n) induc?
           32116  OLIGOMERI?
         3543432  INDUC?
      S2     926  OLIGOMERI? (5N) INDUC?
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             926  S2
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Processing
Processing
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...examined 50 records  (100)
...examined 50 records  (150)
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          315946  LIGAND
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? s s5 and s6
              87  S5
           39878  S6
      S7      12  S5 AND S6
? t s7/3,k,ab/1-12

 7/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10369871   99364310   PMID: 10437622
  Fas-Mediated apoptosis is inhibited by TSH and iodine in moderate
concentrations in primary human thyrocytes in vitro.
  Feldkamp J; Pascher E; Perniok A; Scherbaum W A
  Department of Endocrinology, Heinrich-Heine-University of Dusseldorf,
Germany. feldkamj@uni-duesseldorf.de
  Hormone and metabolic research. Hormon- und Stoffwechselforschung.
Hormones et metabolisme (GERMANY)  Jun 1999,  31  (6)  p355-8,
ISSN 0018-5043   Journal Code: 0177722
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Programmed cell death (apoptosis) can be found in normal thyroid tissue
and in various diseases affecting the thyroid gland. The Fas/Fas
ligand (FasL) system is involved in the induction of apoptosis in
human thyrocytes. Cross-linking the Fas receptor with its own ligand
 or with an antibody capable of oligomerizing with the receptor
induces programmed cell d
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10341123 99343732 PMID: 10415022

Requirements for signal delivery through CD44: analysis using CD44-Fas chimeric proteins.

Ishiwatari-Hayasaka H; Fujimoto T; Osawa T; Hirama T; Toyama-Sorimachi N; Miyasaka M

Department of Bioregulation, Biomedical Research Center, Osaka University Graduate School of Medicine, Suita, Japan.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Aug 1 **1999**, 163 (3) p1258-64, ISSN 0022-1767 Journal Code: 2985117R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

CD44 is a transmembrane glycoprotein involved in various cell adhesion events, including lymphocyte migration, early hemopoiesis, and tumor metastasis. To examine the requirements of CD44 for signal delivery through the extracellular domain, we constructed a chimeric CD44 protein fused to the intracellular domain of Fas on its C-terminus. In cells expressing the CD44-Fas fusion protein, apoptosis could be induced by treatment with certain anti-CD44 mAbs alone, especially those recognizing the epitope group d, which has been previously shown to play a role in **ligand** binding, indicating that ligation of a specific region of the CD44 extracellular domain results in signal delivery. Of note was that appropriate ligation of the epitope h also resulted in the generation of apoptotic signal, although this region was not thought to be involved in **ligand** binding. In contrast, the so-called blocking anti-CD44 mAbs (epitope group f) that can abrogate the binding of hyaluronate (HA) failed to induce apoptosis even after further cross-linking with the secondary Ab, indicating that a mere mAb-**induced oligomerization** of the chimeric proteins is insufficient for signal generation. However, these blocking mAbs were instead capable of inhibiting apoptosis induced by nonblocking mAb (epitope group h). Furthermore, a chimeric protein bearing a mutation in the HA binding domain and hence lacking the ability to recognize HA was incapable of mediating the mAb-induced apoptosis, suggesting that the functional integrity of the HA binding domain is crucial to the signal generation in CD44.

..a transcriptional activation domain; (c) a transcriptional repressor domain; or (d) a signaling domain which **induces** the biological process following **oligomerization** of the chimeric protein to form the **ligand** cross-linke

34. A method for providing a mammal responsive to a selected **ligand** which can regulate the transcription of a target gene in a cell within the mammal...

...1) at least one genetic construct encoding a chimeric protein comprising (a) at least one **ligand**-binding domain which binds to a selected **ligand**, and (b) a heterologous protein domain which regulates transcription of the target gene, wherein the selected **ligand** binds to and oligomerizes two or more chimeric protein molecules to form a **ligand** cross-linked complex and further has one or more of the following characteristics: (i) the **ligand** is not a protein; (ii) the **ligand** has a molecular weight less than 5 kD; and (iii) the **ligand** is membrane permeable, and (2) the target gene under the control of a transcription control element responsive to the **ligand** cross-linked complex.

Non-exemplary Claims: ...comprising at least one genetic construct encoding a chimeric protein comprising (a) at least one **ligand**-binding domain which binds to a selected **ligand**, and (b) a heterologous protein domain which induces the biological process, wherein the selected **ligand** binds to and oligomerizes two or more chimeric protein molecules to form a **ligand** cross-linked complex and further has one or more of the following characteristics: (i) the **ligand** is not a protein; (ii) the **ligand** has a molecular weight less than 5 kD; and (iii) the **ligand** is membrane permeable, and wherein mutual association of two or more of the heterologous protein domains in a **ligand** cross-linked complex induces the biological process; and (B) exposing the cell to the **ligand** in an amount effective to form the **ligand** cross-linked complex and thereby induce the biological process...

ialog Acc No: 3064819 IFI Acc No: 9836954
Document Type: C
REGULATED TRANSCRIPTION OF TARGETED GENES AND OTHER BIOLOGICAL EVENTS; DIMERIZATION, OLIGOMERIZATION OF PROTEINS; ACTIVATION OF CELLMEMBRANE RECEPTORS
Inventors: Belshaw Peter (US); Crabtree Gerald R (US); Schreiber Stuart L (US); Spencer David M (US); Wandless Thomas J (US)
Assignee: Harvard College, President & Fellows of; Stanford, Leland Jr University Trustees
Assignee Code: 00542 49136 Document Type: REASSIGNED
Publication (No,Date), Applic (No,Date):
US 5830462 **19981103** US 95478386 19950607
Publication Kind: A
Calculated Expiration: 20151103
(Cited in 002 later patents)
Cont.-in-part Pub(No),Applic(No,Date): ABANDONED US 9317931 19930212; ABANDONED US 9392977 19930716; ABANDONED US 94179748 19940107; US 94196043 19940211; US 94292597 19940818
Division Pub(No),Applic(No,Date): US 95388653 19950214
Priority Applic(No,Date): US 95478386 19950607; US 9317931 19930212; US 9392977 19930716; US 94179748 19940107; US 94196043 19940211; US 94292597 19940818; US 95388653 19950214

Abstract: Dimerization and oligomerization of proteins are general biological control mechanisms that contribute to the activation of cell membrane receptors, transcription factors, vesicle fusion proteins, and other classes of intra- and extracellular proteins. We have developed a general procedure for the regulated (**inducible**) dimerization or **oligomerization** of intracellular proteins. In principle, any two target proteins can be induced to associate by treating the cells or organisms that harbor them with cell permeable, synthetic ligands. To illustrate the practice of this invention, we have induced: (1) the intracellular aggregation of the cytoplasmic tail of the Zeta chai

Functional blocks in caspase activation pathways are common in leukemia and predict patient response to induction chemotherapy.
Schimmer Aaron D; Pedersen Irene Munk; Kitada Shinichi; Eksioglu-Demiralp Emel; Minden Mark D; Pinto Ryan; Mah Ken; Andreeff Michael; Kim Youngsoo; Suh Won Suk; Reed John C
The Burnham Institute, La Jolla, California 92037, USA.
Cancer research (United States) Mar 15 2003, 63 (6) p1242-8, ISSN 0008-5472 Journal Code: 2984705R
Contract/Grant No.: P01 CA55164-10; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Defects in apoptosis mechanisms contribute to chemoresistance in malignancy. However, correlations of apoptosis-regulating proteins with clinical outcome in cancer patients are variable, presumably reflecting the difficulty of using static tests of gene expression in a scenario influenced by a dynamic interplay of multiple pro- and antiapoptotic molecules. Therefore, we assessed the functional integrity of apoptosis pathways in intact primary leukemia cells and correlated the functional status of these pathways with clinical outcome. Active apoptogenic proteins were introduced into primary leukemia cells by electroporation followed by measurement of active caspases by flow cytometric techniques. Cytochrome c was introduced to activate the intrinsic (mitochondrial) pathway, whereas caspase-8 was introduced to activate the extrinsic (death receptor) pathway. In a series of 24 patients with acute myeloid leukemia, 79% had a block in at least one pathway, indicating that defects in caspase activation mechanisms are common in patients with leukemia. Simultaneous blocks in both pathways correlated with chemoresistant disease (92% of patients with chemoresistant disease versus 33% of patients with chemosensitive disease; P = 0.005) and decreased overall patient survival (35% versus 89% 1-year survival; P = 0.02). Simultaneous blockage of the intrinsic and extrinsic pathways could be explained by a defect **located** at a point of convergence of the two pathways, probably related to overexpression of endogenous **inhibitors** of the effector-**caspases**, rather than decreased levels of these proteases. This study supports the importance of apoptosis pathways in determining response to chemotherapy and suggests that functional defects in caspase activation are prognostic in patients with leukemia.

... 02). Simultaneous blockage of the intrinsic and extrinsic pathways could be explained by a defect **located** at a point of convergence of the two pathways, probably related to overexpression of endogenous **inhibitors** of the effector-**caspases** , rather than decreased levels of these proteases. This study supports the importance of apoptosis pathways...
Descriptors: Caspases--administration and dosage--AD; ***Caspases** --antagonists and **inhibitors**--AI; *Cytochrome c--administration and dosage--AD; *Leukemia, Myeloid--drug therapy--DT; *Leukemia, Myeloid --enzymology...

4/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14572251 22526335 PMID: 12639759
The role of polyol pathway in glucose-induced apoptosis of cultured retinal pericytes.
Miwa Kazuma; Nakamura Jiro; Hamada Yoji; Naruse Keiko; Nakashima Eitaro; Kato Koichi; Kasuya Yasuhide; Yasuda Yutaka; Kamiya Hideki; Hotta Nigishi
The Third Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsuruma-cho, Showa-ku, 466-8550, Nagoya, Japan
Diabetes research and clinical practice (Ireland) Apr 2003, 60 (1)

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? s ricin
      S1    8608  RICIN
? s apoptosis
      S2  251467  APOPTOSIS
? s s1 and s2
            8608  S1
          251467  S2
      S3     212  S1 AND S2
? s caspase??
      S4   41225  CASPASE??
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           41225  S4
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>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
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 6/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

14867430   22194256   PMID: 12204114
   Resistance against ricin-induced apoptosis in a brefeldin
A-resistant mutant cell line (BER-40) of Vero cells.
  Tamura Tadashi; Oda Tatsuya; Muramatsu Tsuyoshi
  Division of Biochemistry, Faculty of Fisheries, Nagasaki University,
Bunkyo-machi, Nagasaki, 852-8521, Japan.
  Journal of biochemistry (Japan) Sep 2002, 132 (3) p441-9, ISSN
0021-924X Journal Code: 0376600
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  We have found that a brefeldin A (BFA)-resistant mutant cell line derived
from Vero cells (BER-40) is highly resistant to ricin-induced
apoptosis as compared with parental Vero cells. In BER-40 cells, all
apoptotic events caused by ricin including cytolysis, nuclear
morphological changes, and DNA fragmentation occur to a lesser extent than
in Vero cells, even though both cell lines show similar sensitivities to
ricin -mediated inhibition of protein synthesis. Furthermore, no
significant apoptotic signaling events, such as increases in caspase
-3 and -9-like activities, release of cytochrome c from mitochondria, or
the cleavage of PARP, were observed in BER-40 cells under the conditions at
which these changes were evident in Vero cells. Intracellular biochemical
changes associated with ricin-induced apoptosis, such as the
depletion of glutathione and an increase in free Zn2+, were also less
apparent in BER-40 cells than in Vero cells. BER-40 cells were also found
to be highly resistant to apoptosis induced by other toxins with
different intoxication mechanisms such as diphtheria toxin, modeccin, and
anisomycin. These results suggest that the entire apoptotic signal
transduction mechanism in BER-40 cells, which may be triggered after the
inhibition of protein synthesis by toxins, becomes resistant. Since MDCK
cells, a naturally BFA resistant cell line, are highly sensitive to
ricin-induced apoptosis , it seems likely that the BFA
resistance phenotype may not necessarily lead to resistance to apoptotic
cell death. Probably the underlaying BFA-resistance mechanism in BER-40
cells is distinct from that in MDCK cells, and the resistance to
ricin-induced apoptosis of BER-40 cells may be a unique
```

phenotype acquired concomitantly with BFA-resistance.

Resistance against **ricin**-induced **apoptosis** in a brefeldin A-resistant mutant cell line (BER-40) of Vero cells.
... BFA)-resistant mutant cell line derived from Vero cells (BER-40) is highly resistant to **ricin**-induced **apoptosis** as compared with parental Vero cells. In BER-40 cells, all apoptotic events caused by **ricin** including cytolysis, nuclear morphological changes, and DNA fragmentation occur to a lesser extent than in Vero cells, even though both cell lines show similar sensitivities to **ricin**-mediated inhibition of protein synthesis. Furthermore, no significant apoptotic signaling events, such as increases in **caspase**-3 and -9-like activities, release of cytochrome c from mitochondria, or the cleavage of...

... conditions at which these changes were evident in Vero cells. Intracellular biochemical changes associated with **ricin**-induced **apoptosis** , such as the depletion of glutathione and an increase in free Zn2+, were also less...

... than in Vero cells. BER-40 cells were also found to be highly resistant to **apoptosis** induced by other toxins with different intoxication mechanisms such as diphtheria toxin, modeccin, and anisomycin...

... becomes resistant. Since MDCK cells, a naturally BFA resistant cell line, are highly sensitive to **ricin**-induced **apoptosis**, it seems likely that the BFA resistance phenotype may not necessarily lead to resistance to...
... in BER-40 cells is distinct from that in MDCK cells, and the resistance to **ricin**-induced **apoptosis** of BER-40 cells may be a unique phenotype acquired concomitantly with BFA-resistance.
Descriptors: **Apoptosis**--drug effects--DE; *Brefeldin A --pharmacology--PD; *Drug Resistance--genetics--GE; *Mutation; *Protein Synthesis Inhibitors--pharmacology--PD; ***Ricin**--toxicity--TO; Antineoplastic Agents--pharmacology--PD; Blotting, Western; **Caspases** --metabolism--ME; Cercopithecus aethiops; Cytochrome c--metabolism--ME; Dogs; Mitochondria--drug effects--DE; Mitochondria--enzymology...
...Enzyme No.: 30 (Poly(ADP-ribose) Polymerases); EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**)
Chemical Name: Antineoplastic Agents; Protein Synthesis Inhibitors; Brefeldin A; Cytochrome c; **Ricin**; Poly(ADP-ribose) Polymerases; CPP32 protein; **Caspases**

6/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13893867 22031533 PMID: 12036057
Comparison of the **apoptosis**-inducing abilities of various protein synthesis inhibitors in U937 cells.
Kageyama Ai; Kusano Izumi; Tamura Tadashi; Oda Tatsuya; Muramatsu Tsuyoshi; et al
Division of Biochemistry, Faculty of Fisheries, Nagasaki University, Japan.
Bioscience, biotechnology, and biochemistry (Japan) Apr 2002, 66 (4) p835-9, ISSN 0916-8451 Journal Code: 9205717
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We compared the abilities of **ricin** , diphtheria toxin, cycloheximide, and anisomycin to induce **apoptosis** , using human myeloid leukemia U937 cells at the concentration of each toxin at which almost complete protein synthesis inhibition was attained within 3 h. Among

these toxins, anisomycin was found to be the most potent **apoptosis** inducer. After a 6-h exposure to anisomycin (1 microg/ml), nearly 95% of the cells had apoptotic nuclear morphological changes, while 53%, 30%, and 10% of the cells showed apoptotic changes after exposure to **ricin** (0.1 microg/ml), diphtheria toxin (10 microg/ml), and cycloheximide (10 microg/ml), respectively. Furthermore, a rapid increase in **caspase** -3-like activity was observed in anisomycin-treated cells. A similar increase in **caspase**-3-like activity was also observed in **ricin** -treated cells on a slower time schedule. However, only a slight increase in the protease activity was induced by diphtheria toxin or cycloheximide even after 6 h of incubation. Since both **ricin** and anisomycin are known to act on 28S ribosomal RNA, our results suggest that this action mechanism may be responsible for their potent **apoptosis** induction, and protein synthesis inhibition alone is not sufficient to induce **apoptosis**.

Comparison of the **apoptosis**-inducing abilities of various protein synthesis inhibitors in U937 cells.

We compared the abilities of **ricin** , diphtheria toxin, cycloheximide, and anisomycin to induce **apoptosis** , using human myeloid leukemia U937 cells at the concentration of each toxin at which almost...

... attained within 3 h. Among these toxins, anisomycin was found to be the most potent **apoptosis** inducer. After a 6-h exposure to anisomycin (1 microg/ml), nearly 95% of the...
... changes, while 53%, 30%, and 10% of the cells showed apoptotic changes after exposure to **ricin** (0.1 microg/ml), diphtheria toxin (10 microg/ml), and cycloheximide (10 microg/ml), respectively. Furthermore, a rapid increase in **caspase** -3-like activity was observed in anisomycin-treated cells. A similar increase in **caspase** -3-like activity was also observed in **ricin**-treated cells on a slower time schedule. However, only a slight increase in the protease...

... was induced by diphtheria toxin or cycloheximide even after 6 h of incubation. Since both **ricin** and anisomycin are known to act on 28S ribosomal RNA, our results suggest that this action mechanism may be responsible for their potent **apoptosis** induction, and protein synthesis inhibition alone is not sufficient to induce **apoptosis**.

Descriptors: **Apoptosis**--drug effects--DE; *Protein Synthesis Inhibitors--pharmacology--PD; Anisomycin--pharmacology--PD; **Apoptosis** --physiology--PH; Cycloheximide--pharmacology--PD; Diphtheria Toxin --pharmacology--PD; Kinetics; **Ricin**--pharmacology--PD; Tumor Cells, Cultured; U937 Cells

Chemical Name: Diphtheria Toxin; Protein Synthesis Inhibitors; Anisomycin ; Cycloheximide; **Ricin**

6/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11988792 99434137 PMID: 10502680

Specific efflux of glutathione from the basolateral membrane domain in polarized MDCK cells during **ricin**-induced **apoptosis**.

Oda T; Sadakata N; Komatsu N; Muramatsu T

Division of Biochemistry, Faculty of Fisheries, Nagasaki University, Bunkyo-machi, Nagasaki, 852-8521, Japan. t-oda@net.nagasaki-u.ac.jp

Journal of biochemistry (JAPAN) Oct 1999, 126 (4) p715-21, ISSN 0021-924X Journal Code: 0376600

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Although the depletion of reduced glutathione (GSH) has been observed in a variety of apoptotic systems, little is known about the mechanism of GSH depletion. In this study we used polarized MDCK cells to study the GSH flux during **ricin**-induced **apoptosis** . Here we report that the specific accumulation of GSH occurred in the basolateral medium during **ricin** treatment with similar kinetics to in apoptotic changes such as an increase in **caspase**-3 like activity and DNA fragmentation, while there was no significant increase in the GSH level in apical medium. These results suggest that GSH efflux occurred through a GSH-specific channel or transporter located in the basolateral membrane domain of polarized MDCK cells undergoing **apoptosis**. Treatment with other protein toxins such as modeccin, Pseudomonas toxin, and diphtheria toxin, which can induce apoptotic cell death, also resulted in selective GSH efflux from the basolateral side. Thus, GSH efflux through a specific transporter may be a common step of **apoptosis** induced by these toxins, while these toxins have different intoxication mechanisms leading to protein synthesis inhibition. Pretreatment of cells with Z-Asp-CH(2)-DCB, a **caspase** family inhibitor, inhibited **ricin**-induced basolateral GSH efflux as well as DNA fragmentation, suggesting that the activation of **caspases** , i.e. those that are inhibited by Z-Asp-CH(2)-DCB, is implicated in the opening of the GSH transporter.

Specific efflux of glutathione from the basolateral membrane domain in polarized MDCK cells during **ricin**-induced **apoptosis**.
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Descriptors: **Apoptosis**--physiology--PH; *Glutathione--metabolism --ME; **Apoptosis**--drug effects--DE; Aspartic Acid --analogs and derivatives--AA; Aspartic Acid--pharmacology--PD; Biological Transport, Active--drug effects--DE; **Caspases**--antagonists and inhibitors--AI; **Caspases**--metabolism--ME; Cell Line; Cell Membrane--metabolism--ME; Cell Polarity; Cysteine Proteinase Inhibitors--pharmacology--PD; Dogs; Kinetics; **Ricin**--toxicity--TO
Enzyme No.: EC 3.4.22.- (**Caspases**)
Chemical Name: Cysteine Proteinase Inhibitors; benzyloxycarbonyl-Asp-CH2O C(O)-2,6-dichlorobenzene; Aspartic Acid; Glutathione; **Ricin**; **Caspases**

6/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11860179 99301382 PMID: 10374846
Diphtheria toxin fused to granulocyte-macrophage colony-stimulating factor and Ara-C exert synergistic toxicity against human AML HL-60 cells.
Kim C N; Bhalla K; Kreitman R J; Willingham M C; Hall P; Tagge E P; Jia T ; Frankel A E

Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA.

Leukemia research (ENGLAND) Jun 1999, 23 (6) p527-38, ISSN 0145-2126 Journal Code: 7706787

Contract/Grant No.: CA56613; CA; NCI; CA63382; CA; NCI; CA76178; CA; NCI; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Human granulocyte-macrophage colony-stimulating factor fused to truncated diphtheria toxin (DT388-GM-CSF) sensitized wild-type and Bcl2-overexpressing HL60 human leukemia cells to intoxication by Ara-C based on proliferation and clonogenic assays. The toxin/drug combination showed dramatic synergistic toxicity with combination indices of < 0.1. Synergy was not seen with two other protein synthesis inhibiting drugs--**ricin** and cycloheximide nor with GMCSF alone. No changes in Ara-C incorporation into cellular DNA or cell cycle occupancy were seen. As compared to exposure to DT388-GM-CSF or Ara-C alone, co-treatment produced significant increases in cytosolic accumulation of cytochrome c, a higher percentage of cells with loss of mitochondrial membrane potential and an increase in reactive oxygen species and morphologic changes of **apoptosis** , and a greater induction of poly(ADP-ribose) polymerase (PARP) and DNA fragmentation factor 45 (DFF45) cleavage activities of **caspase** 3. Co-treatment did not significantly alter Bcl2, Bcl-xL, Bax or Fas receptor (FasR), but modestly increased Fas ligand (FasL) protein. These finding suggest that co-treatment with DT388-GM-CSF may lead to a lowered apoptotic threshold and clonogenic survival of human AML blasts due to Ara-C. These observations also suggest that clinical trials of combination therapy may be warranted in patients with AML.

... indices of < 0.1. Synergy was not seen with two other protein synthesis inhibiting drugs--**ricin** and cycloheximide nor with GMCSF alone. No changes in Ara-C incorporation into cellular DNA...

... of mitochondrial membrane potential and an increase in reactive oxygen species and morphologic changes of **apoptosis**, and a greater induction of poly(ADP-ribose) polymerase (PARP) and DNA fragmentation factor 45 (DFF45) cleavage activities of **caspase** 3. Co-treatment did not significantly alter Bcl2, Bcl-xL, Bax or Fas receptor (FasR...

6/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11770746 99208997 PMID: 10192917

Involvement of N-acetylcysteine-sensitive pathways in **ricin**-induced apoptotic cell death in U937 cells.

Oda T; Iwaoka J; Komatsu N; Muramatsu T

Division of Biochemistry, Faculty of Fisheries, Nagasaki University, Japan. t-oda@net.nagasaki-u.ac.jp

Bioscience, biotechnology, and biochemistry (JAPAN) Feb 1999, 63 (2) p341-8, ISSN 0916-8451 Journal Code: 9205717

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have found that the antioxidant N-acetylcysteine (NAC) strongly inhibited **ricin** -induced apoptotic cell death in U937 cells (human myeloid leukemia), as judged by cytotoxicity, nuclear morphological change, and DNA fragmentation. Consistent with these observations, a significant depletion of cellular glutathione was observed in **ricin**-treated cells, and NAC prevented the decrease in cellular glutathione. On the other

hand, among the **caspase** inhibitors tested, Z-Asp-CH2-DCB, which inhibited **ricin** cytotoxicity, also suppressed **ricin**-mediated glutathione depletion, while NAC did not affect the generation of **caspase**-3 like activity in **ricin**-treated cells. These results suggest that glutathione loss takes place downstream from **caspase** activation during the **ricin** -induced apoptotic process. Treatment with a specific inhibitor of glutathione biosynthesis, buthionine sulfoximine (BSO) failed to induce **apoptosis**, and had no effect on the overall extent of **ricin**-induced **apoptosis**, even though the glutathione level was decreased to less than 5% of the control level. However, NAC still protected against **ricin**-induced **apoptosis** in the BSO-treated cells. We conclude that glutathione loss is one of several apoptotic changes caused by **ricin**, but is not a sufficient factor for the progress of **apoptosis**. NAC may prevent **ricin**-induced **apoptosis** through maintaining an intracellular reducing condition by acting as a thiol supplier.

Involvement of N-acetylcysteine-sensitive pathways in **ricin**-induced apoptotic cell death in U937 cells.

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... DNA fragmentation. Consistent with these observations, a significant depletion of cellular glutathione was observed in **ricin**-treated cells, and NAC prevented the decrease in cellular glutathione. On the other hand, among the **caspase** inhibitors tested, Z-Asp-CH2-DCB, which inhibited **ricin** cytotoxicity, also suppressed **ricin**-mediated glutathione depletion, while NAC did not affect the generation of **caspase**-3 like activity in **ricin**-treated cells. These results suggest that glutathione loss takes place downstream from **caspase** activation during the **ricin** -induced apoptotic process. Treatment with a specific inhibitor of glutathione biosynthesis, buthionine sulfoximine (BSO) failed to induce **apoptosis**, and had no effect on the overall extent of **ricin**-induced **apoptosis**, even though the glutathione level was decreased to less than 5% of the control level. However, NAC still protected against **ricin**-induced **apoptosis** in the BSO-treated cells. We conclude that glutathione loss is one of several apoptotic changes caused by **ricin**, but is not a sufficient factor for the progress of **apoptosis**. NAC may prevent **ricin**-induced **apoptosis** through maintaining an intracellular reducing condition by acting as a thiol supplier.

Descriptors: Acetylcysteine--pharmacology--PD; *Antioxidants--pharmacology--PD; ***Apoptosis**--drug effects--DE; *Free Radical Scavengers --pharmacology--PD; ***Ricin**--metabolism--ME; Acetylcysteine--metabolism--ME; Antioxidants--metabolism--ME; **Apoptosis**--physiology--PH; Buthionine Sulfoximine--pharmacology--PD; **Caspases**--antagonists and inhibitors--AI; Cell Survival--drug effects--DE; Cell Survival--physiology --PH; DNA Fragmentation...

Enzyme No.: EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (**Caspases**)

Chemical Name: Antioxidants; Enzyme Inhibitors; Free Radical Scavengers; Protein Synthesis Inhibitors; Buthionine Sulfoximine; Acetylcysteine; Glutathione; **Ricin**; CPP32 protein; **Caspases**

6/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11621842 99055169 PMID: 9836586

Role of **caspases** in immunotoxin-induced **apoptosis** of cancer cells.

Keppler-Hafkemeyer A; Brinkmann U; Pastan I